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Vol. II NOVEMBER, 1930 No. 1

THE JOURNAL OF ALLERGY

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OFFICIAL ORGAN OF
THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS
THE ASSOCIATION FOR THE STUDY OF ALLERGY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523 PINE BOULEVARD,
ST. LOUIS, U. S. A.

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The Journal of Allergy

CONTENTS FOR NOVEMBER, 1930

Dust Hypersensitiveness with Special Reference to Castor Bean. By Bret Ratner, M.D., New York, N. Y. ---- 1

Studies on Pollen and Pollen Extracts. IV. The Allergically Active Constituent in Pollen Oil. By Marjorie B. Moore, Ph.D., Hobart W. Cromwell, Sc.D., and Edmond E. Moore, Ph.D., Indianapolis, Ind. ---- 6

Trichophytin Hypersensitiveness of Urticarial Type, with Circulating Antibodies and Passive Transference. By Marion B. Sulzberger, M.D., and Phyllis S. Kerr, M.D., New York, N. Y. ---- 11

The Heart in Bronchial Asthma. By Leon Unger, S.B., M.D., Chicago, Ill. ---- 17

The Variability of Skin Reactions in Allergy. By H. L. Alexander, M.D., and F. S. McConnell, A.B., St. Louis, Mo. ---- 23

A Clinical Study of the Use of Calcium in Controlled Cases of Allergy. By Milton B. Cohen, M.D., and J. A. Rudolph, M.D., Cleveland, Ohio ---- 34

Studies in Allergy. II. A Case of Sensitiveness to Cuttlefish Bone. By Clifford G. Weston, M.D., Glen Ridge, N. J. ---- 37

The Continuous Method of Hay Fever Treatment. By Karl D. Figley, M.D., Toledo, Ohio ---- 39

A Nasal Test with Dry Pollens in the Diagnosis of Seasonal Hay Fever. By B. G. Efron, M.D., and W. T. Penfound, A.M., New Orleans, La. ---- 43

A Critical Analysis of the Information Obtained from Hay-Fever Sufferers. By Harry L. Huber, M.D., Chicago, Ill. ---- 48

Relief of Bronchial Asthma Following Lobar Pneumonia. By Samuel Berg, M.D., Newark, N. J. ---- 54

Case Report Illustrating the Nonspecific Induction of Local and General Reactions in a Hay Fever (Syphilitic) Patient by the Intravenous Injection of Neosol. By A. H. W. Caulfeild, M.B., Toronto, Ontario ---- 60

Selected Abstracts ---- 62

Medical
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The Journal of Allergy

VOL. II NOVEMBER, 1930 No. 1

Original Articles

DUST HYPERSENSITIVENESS WITH SPECIAL REFERENCE TO CASTOR BEAN*†

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NEW YORK, N. Y.

IN THE study of castor bean dust hypersensitiveness we have an especially interesting phase of the dust problem in general. It is an unusual substance, and the instances in which individuals come in contact with it demonstrate the insidious manner in which antigenic dusts may be the inciting cause of allergic manifestations. The correlation with animal experimentation is singular.

Bernton[1] in 1923 reported the case of an individual who worked in the laboratory of the U. S. Bureau of Agriculture for a period of three years with no ill effects. After that time, however, he developed symptoms of sneezing, lacrimation and sweating of the forehead, etc. In the army for a period of two years he was absolutely free from attacks. Upon his return to the laboratory, he again developed these symptoms. Skin tests with an extract of castor bean were positive, and Bernton concluded that occupational sensitization to castor bean is a definite condition.

A few months later, Robbins[2] reported the case of a student who, when working with the castor bean, developed apparent attacks of hay fever which became progressively more frequent and severe. It was then discovered that castor bean was the cause of the condition. The effect of the plant itself was similar to that of the bean. There was another instructor whose symptoms were entirely limited to the eyes.

Shortly after that, Snell[3] reported his own case of hypersensitiveness to castor bean. He stated that for years he handled the castor bean with impunity until one day he developed a severe attack of hay fever and violent itching of the skin. His attacks of hay fever occurred only in the laboratory the first three days of the week when he taught the

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†This work is being carried on under the Crane Fund for the Study of Allergic Diseases in Children.

freshmen and handled the castor bean. When he finally correlated these attacks with the castor bean, he removed it from the laboratory and was relieved of all symptoms. Some time later while dried castor bean seeds were being emptied into another bottle by an assistant, Snell began to sneeze.

Later, Arnold[4] reported that in Honolulu where natives eat castor bean with apparent impunity, a soldier stationed there ate five castor beans. He developed acute anaphylactic symptoms a few hours after ingestion and died the following day in coma. Arnold also reported that since then he observed two cases in which the ingestion of a single bean was followed in five minutes by edema of the mouth and pharynx, in one case accompanied by diffuse edema of the glottis. These symptoms were relieved by adrenalin.

In the following year Follweiler and Haley[5] reported three cases from the Department of Agriculture at Pennsylvania State College, where they were working with ricinous lipase extracted from the castor bean. In one of these cases, an instructor developed what appeared to be a severe cold with violent and continuous sneezing and coughing and edema of the mucous membranes of the nose, throat, eyes and ears, together with a dull headache and watering of the eyes. The condition gradually grew worse, and he developed severe asthmatic symptoms. These symptoms were accompanied by generalized joint pains and nocturnal paroxysms of suffocation with labored breathing, and in addition, marked intestinal pains with alternate diarrhea and constipation. He lost weight and gradually became prostrated. When going into the open air he improved markedly, and between Saturday noon and Monday morning he had a period of relief, but on entering the laboratory, his symptoms recurred. One day, while demonstrating and sifting some castor bean lipase preparation, he became so affected that it was impossible for him to breathe. It was then suspected that he was sensitive to castor bean. When the castor bean problem was discontinued and the laboratory thoroughly cleaned, he regained his health.

Figley and Elrod[6] in 1928 reported the occurrence of endemic asthma which was finally traced to castor bean dust thrown off by a castor oil factory. Eighty-five persons living within a radius of a mile of this oil mill ascribed their asthmatic attacks to its presence. The authors examined thirty-two of these; two proved to be cases of seasonal hay fever, the remaining thirty gave the following similar histories: They had lived in the vicinity of the mill for varying lengths of time. None of them had asthma before moving into the district, and the onset of the attacks varied from one to seventeen years after moving into the neighborhood. The attacks were nocturnal in the men who worked during the day at a distance from their homes, but occurred day or night in the housewives and children whose work did

not take them away from the vicinity. Attacks were most frequent and most severe during the fall and spring months when the wind attained its highest velocity. The mill was in operation day and night except during June, July and August, and it was during these months that the patients were most free from attacks. Many of these patients found that they could obtain relief by leaving the neighborhood, but that the asthma recurred when they returned to their homes. If they went on vacations or moved away from the mile radius of the mill, their attacks disappeared. Positive skin reactions to castor bean dust were obtained in all cases. To eliminate the possibility of the reaction being due to the irritating effect of ricin, control tests were done on forty persons with negative results.

Castor bean dust recovered from the air was shown to consist of particles about the size of ragweed pollen, which explains the ease with which the wind carries this dust. This is in contrast with flaxseed in which instance, after the expression of linseed oil, 9 per cent of the oil still remains, making it too heavy to be wind-borne.

COMMENT

A number of years ago we voiced the belief that asthma could be acquired through the inhalation of an antigenic dust; the situation described by Figley and Elrod therefore interested us considerably. Our original experiments[7] were concerned with the problem of demonstrating that an antigenic dust in a dry state could act as a sensitizing agent, entry into the body being gained through the nasal mucosa.

Guinea pigs were exposed in an especially constructed apparatus (dust chamber) to dry horse-dander dust floating in the air. After a suitable incubation period, the animals were again exposed in these chambers. Symptoms of grave anaphylaxis were manifested which so resembled the symptom complex of bronchial asthma that we termed the syndrome "respiratory anaphylaxis" as opposed to anaphylaxis induced by parenteral injection. Each time animals thus sensitized were exposed the symptoms were reproduced. Recovery was hastened with epinephrine which further correlated respiratory anaphylaxis with asthma in the human being.

We believe that by this method we have devised a means of studying the anaphylactogenic properties of dusts experimentally in a manner which most closely simulates conditions to which the human being is subject, and which may be considered natural as compared with the artificial method when antigen is introduced by parenteral injection.

We therefore applied this method to the study of the anaphylactogenic properties of castor bean dust.[8] We first learned that this dust contains a primary toxic element, ricin, which affected the abdominal viscera[9] and, in addition, produced a severe pulmonary condition. We showed that if this ricin toxicity is sudden and overwhelming, it may

result in severe toxemia or even death, which was also noted in one of the above reports. But if the ricin is inhaled in small amounts, a gradual immunity will develop. After much of the ricin was extracted, we succeeded in sensitizing our animals by inhalation and demonstrated the establishment of respiratory anaphylaxis (asthma). The toxic effects of the ricin are easily distinguished from the anaphylactic symptoms.

The striking fact which is apparent from a comparison of cases cited from the literature and our experimental work is, therefore, that the same method of exposure in animal and man is capable of producing similar results, namely, that the continuous inhalation of such a dust as castor bean is capable of producing both toxic manifestations and anaphylactic sensitization. In other words, continued contact with an antigenic dust will cause the development of a sensitization to that specific dust in the case of susceptible individuals. We are not prepared to state what renders an individual susceptible. Many hypotheses have been offered but none so far has been proved adequate. We must grant, however, that there exists such a susceptibility, since not all individuals, not all animals under similar circumstances develop hypersensitiveness. Such being the case, we must recognize the possibility of the development of sensitization to various dusts encountered in the industries, as well as in homes, schools, etc. Until the basic cause for such susceptibility is discovered, in which event the individual may be able to cope with proteins, the only hope for any preventive measures in respiratory allergic conditions is to eliminate antigenic dusts from the environment, or possibly some manner may be discovered to render such dusts nonanaphylactogenic.

CONCLUSIONS

There is growing evidence in the literature that contact with antigenic dusts may establish hypersensitiveness in susceptible individuals. The literature on castor bean sensitization offers an interesting situation for the study of this problem. Reports have been made on the development of such hypersensitiveness in isolated individuals working particularly in botanical laboratories. The occurrence of endemic asthma in a community, due to this dust, has been described. The situation was duplicated experimentally in the guinea pig. The correlation of the findings in these situations we believe tends to support our original hypothesis that an antigenic dust in a dry state can act as a sensitizing agent, entry into the body being gained through the nasal mucosa. We therefore believe that dusts produced in industries, etc., may be significant factors in the production of certain respiratory allergic manifestations. We have suggested that the study of the dust problem may be facilitated by a method we have described, and that pre-

ventive measures against the inception of sensitization to specific antigenic dusts may eventuate from such a study.

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STUDIES ON POLLEN AND POLLEN EXTRACTS
IV. THE ALLERGICALLY ACTIVE CONSTITUENT IN POLLEN OIL*

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A RECENT paper by Milford[1] has called attention to the specific activity of that portion of ragweed pollen which is extracted by the ordinary fat solvents. His careful work has practically ruled out the possibility of contamination with moisture and thus with water-soluble constituents.

In many processes for preparing pollen extracts the ether-soluble fraction is discarded. Most investigators have completely disregarded it when attempting to determine the active constituent in pollen. It has been empirically ascertained that extracts of pollen made with a menstruum containing glycerol are often more active, and this may now be explained on the basis of extraction of a considerable portion of oil by the glycerol.

In this laboratory a considerable quantity of ether extract from giant ragweed pollen had been saved for study. It was purified and used for tests on ragweed-susceptible patients by the scratch method. Our results agree quite closely with those of Milford, fifteen positive reactions being obtained with the whole fat in a total of twenty-seven patients tested.

METHOD AND RESULTS

For purification, the ether was evaporated from the extract and the oily residue heated at 120° C. to free it from any moisture. This was then redissolved in anhydrous ether, filtered through a dry paper, centrifuged, and the solution again evaporated and dried. In one sample a further purification was effected by means of solution in petroleum ether.

The purified fatty material was dissolved in anhydrous ether, placed in a thin rubber membrane, and dialyzed against ether.[2] The dialysis was carried out at about 2° to 5° C., with daily changes of the ether outside until it remained practically colorless. The substances both inside and outside the membrane were saved.

The dialyzable fraction, when freed from ether and dried, had an

*From the laboratories of the Swan-Myers Company, Indianapolis.

appearance very similar to that of the original pollen oil. It was used for clinical tests in the dried condition.

Inside the membrane, during the course of dialysis, a light-colored waxy material had precipitated. This could not be completely dissolved by the addition of more ether. Addition of alcohol caused a cloudiness in the entire solution. The solvent was completely evaporated, and the residue dried at 110° C. and suspended in water or physiologic salt solution. It formed a cloudy suspension of so fine a state of dispersion that it was very slow in settling. This suspension was used for testing by either the scratch or intradermal method.

Tests were made on twenty patients who gave pronounced reactions, by the scratch method of testing, to a glycero-saline extract of giant ragweed pollen. Ten of these exhibited positive reactions to the whole oil by the same method of testing, while in no case was a positive reaction obtained from the dialyzable oil fraction. The suspension of the nondialyzable fraction from the oil showed a positive reaction in every case tested in which the whole fat was active.

Of twelve cases sensitive to the stock ragweed, ten gave definitely positive tests with the nondialyzable fraction from the oil, and two gave doubtful reactions. In four of these ten cases reactive to the nondialyzable oil fraction, the reaction to the whole oil was negative or doubtful.

It thus appears that the active constituent of the oil from giant ragweed pollen is nondialyzable from ether solution through a rubber membrane. Its colloidal nature is confirmed by the fact that the original ether solution of the oil gives a distinct Tyndall cone, while that of the dialyzable fraction exhibits this phenomenon scarcely at all.

The whole oil from giant ragweed pollen is readily suspended in water or salt solution to give a fairly permanent emulsion; whereas the dialyzable fraction is suspended with difficulty and separates at once.

The chemical nature of the active nondialyzable constituent is as yet undetermined, although certain preliminary tests have been made. Its water suspension gives a strongly positive Molisch test, no color with ferric chloride solution, and a distinct reddish-amber color when dissolved in cold concentrated sulfuric acid. These tests indicate that it may be glucosidic in nature, and this concept is further strengthened by its behavior with Fehling's solution. No reduction occurs on addition of the suspension to hot Fehling's solution. Reduction does take place, however, after prolonged heating of the mixture on a water-bath. Addition of the hydrolysate prepared by heating the suspension with 5 per cent sulfuric acid causes immediate reduction of hot Fehling's solution.

The water suspension of nondialyzable material from the oil gives no reaction for protein by the biuret or Millon's tests. Milford[1] re-

ports no nitrogen or phosphorus in the ragweed pollen oil. The presence of nitrogen could be demonstrated here by means of a micro-Kjeldahl digestion with subsequent Nesslerization.

The apparent presence of considerable carbohydrate in this active nondialyzable material from the oil fraction of the pollen lends new interest to the fact that all the active fractions prepared here from aqueous extracts (presumably proteose, albumin-proteose, and globulin) have reacted positively to the Molisch test.

ALLERGIC REACTIONS

The method of local passive sensitization was used to study the relationship of the nondialyzable fraction from the oil to the water-soluble antigens of the pollen. Six normal subjects and two different sera from ragweed sensitive individuals were used for these experiments. The aqueous fractions used correspond in method of preparation with those prepared for the quantitative work reported in the first paper of this series.[3] The proteose solution was prepared by boiling the dialyzed water solution after slight acidification with acetic acid, and subsequent filtration. All the solutions were passed through a Berkefeld filter before being used for intradermal testing. The suspension of the nondialyzable oil fraction was made in sterilized physiologic salt solution containing 0.5 per cent chlorbutanol.

Milford[1] has reported activity to the water extract of pollen in passively sensitized sites which had been exhausted to the oil. The work here confirmed this observation, and indicated that the additional antigen in the aqueous extract is present in the albumin fraction. Sites desensitized to the nondialyzable material from the oil were found not to react to the globulin or proteose fractions of the pollen but did react to the albumin-proteose. Sites desensitized to these three aqueous fractions gave no reaction to the nondialyzable oil fraction, although it was very active to other sites on the same individuals sensitized with the same serum.

Ether-soluble fractions were also prepared from short ragweed and timothy pollens. The short ragweed pollen oil was similar in appearance and activity to that from giant ragweed. On dialysis, it gave a precipitate inside the sac which reacted positively to the Molisch test and negatively to the Millon test. The suspension of this precipitate in physiologic salt solution gave pronounced reactions in skin sites passively sensitized with ragweed-sensitive serum.

The timothy oil was much more solid in consistency than that from the ragweeds, and was quite light colored. On dialysis of its ether solution a precipitate was formed inside the membrane which appeared as a light fine powder after evaporation of the ether. This material would not form a fairly stable suspension in water, as did the similar

fraction from giant ragweed pollen. By shaking, however, it was possible to suspend it for testing. This suspension gave a strongly positive Molisch test.

The whole timothy oil was tested on two timothy-sensitive patients and did not give a definitely positive reaction in either case. The serum of one of these patients was obtained for passive sensitization, and the sites were found to give no reaction with a suspension of the nondialyzable fraction from the oil.

A study of timothy oil and its nondialyzable fraction should be made on a large number of patients. Milford[1] was able to obtain positive reactions to the whole timothy oil in some cases, and, by analogy, the nondialyzable fraction of this oil might be expected to contain the active constituent.

DISCUSSION

From the results of the experiments mentioned here, it appears that the active constituent of giant ragweed pollen oil is wholly contained in the nondialyzable portion. Since it appears to be identical with one or more of the antigens soluble in aqueous solvents, the question arises as to the cause of its presence in the material extracted with fat solvents. The present information on the subject appears to support the theory that the particles of active substance in the pollen grain may be partially covered with a coating of fatty substance. When the fat solvent is added, the particles which contain a sufficient coating of soluble material will be extracted and will remain in suspension so long as this coating continues to adhere. These suspended particles are responsible for the Tyndall cone observed in the ether extract. Dialysis gradually removes the fatty coating, and the particles of nondialyzable active material are precipitated. The insolubility of this constituent, when thus separated, in water or dilute saline solution may be due to "denaturation" during the process of drying the fat. This question should receive further study.

SUMMARY

1. Ether-soluble fractions from the pollens of giant and short ragweed and timothy have been prepared, dried, redissolved in ether and dialyzed in a rubber sac against ether. In the case of the giant ragweed pollen it has been established that the skin-reacting activity resides in the nondialyzable fraction.

2. By the method of local passive sensitization and exhaustion of sites, it appears that the active constituent in the pollen oil is identical with one or more of the antigens extracted by aqueous solvents. A theory is advanced to account for its presence in the material extracted by fat solvents.

3. Certain chemical reactions of the nondialyzable fraction from the oil have been studied, and a similarity to those of the active aqueous fractions has been pointed out.

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TRICHOPHYTIN HYPERSENSITIVENESS OF URTICARIAL TYPE, WITH CIRCULATING ANTIBODIES AND PASSIVE TRANSFERENCE

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A DETAILED review of the voluminous and somewhat contradictory and confusing literature on trichophytin allergy seems unnecessary for the purposes of this short report. Those interested are referred to Bruno Bloch's[1] summary of the present situation. Only a few points with direct bearing on our experiments must be here recalled.

Trichophytin is prepared from different strains and varieties of pathogenic hyphomycetes and usually contains (*a*) the endo- and exotoxins of the fungi, (*b*) their nontoxic constituents (body structure, protoplasm, salts, etc.), (*c*) the culture medium in which they have been grown (agar-agar, crude maltose or glucose, beef broth, peptone, etc.) and (*d*) some form of preservative or disinfectant.

Since Plato-Neisser first employed trichophytin, many authors have added to our knowledge of the hypersensitiveness to this substance. This hypersensitiveness is present in certain cases of mycotic infections in human beings.

The observations of European workers have shown that the hypersensitiveness to trichophytin is "group specific"; that is, in human beings it occurs (exclusively) in persons who have or have had tinea infections, but test with the products of one fungus will give positive results even though the infection has been actually caused by another. For instance, a man suffering from tinea of the beard caused by *Trichophyton gypseum* may react to injections of trichophytin prepared from *Achorion quinckeanum*.

Until comparatively recently it was thought that only the deep infections (sycosis, kerion celsi, granuloma Majocchi) led to skin hypersensitiveness to trichophytin with any degree of constancy. However, the recent work of Werner Jadassohn and Samuel Peck[2] (in Bloch's Clinic in Zürich) and of Sulzberger and Lewis[3] has shown that this skin hypersensitiveness is also almost constantly present in the superficial infection known as tinea or ringworm or epidermophytosis of the feet.*

*We wish here to interpolate a remark not in absolute relationship to the subject matter. It seems to us that the frequency of tinea of the feet in America, as compared to Europe, and the frequency of the allergic change of the skin due to this infection, explain the great numbers of positive skin reactions to intradermal injection of trichopytin which one finds in American, as compared with European patients. This has naturally led to the diminished belief in the diagnostic value of trichophytin in the United States; for a procedure which gives a large number of positives in apparently normal individuals cannot bear much weight in diagnosis. In Europe ringworm of the feet is still so infrequent that positive trichophytin reactions are almost pathognomonic of deep-seated tinea or kerion of the hairy surfaces.

The usual type of trichophytin test which has been employed is the intradermal reaction, which, if positive, causes an inflammatory zone to appear at the injection site twenty-four to forty-eight hours later. It will be seen that this test resembles the tuberculin test of Mendel-Mantoux. In analogy with other tuberculin reactions, the Moro test has also been performed with trichophytin, particularly in trichophytids (J. Jadassohn). A somewhat new method of testing was recently described by Sulzberger and Lewis,[3] who employed the trichophytin patch or contact test, and observed positive reactions of eczematous type twenty-four to forty-eight or more hours after the application of the patch.

On account of the great theoretical as well as practical importance, but perhaps more particularly on account of the striking analogies of trichophytin and tuberculin allergy, many attempts have been made to demonstrate circulating antibodies to trichophytin. Some of these have met with success. In hypersensitive human beings, precipitins, agglutinins, and complement-fixation antibodies were demonstrated among others by Widal, Abrami, Joltrain, Weill, Truffi, Capelli, Pecori, and in extensive experiments by Blumenthal and Haupt.[4] In addition to this, Max Jessner[5] demonstrated that the blood serum of hypersensitive human beings contained substances which inhibited the growth of fungi in vitro.

While no antibodies of the above types could be found in animals, Martenstein[6] discovered that there were certain specific substances in both the skin and the serum of guinea pigs experimentally infected with pathogenic fungi. When these substances were brought into contact with the fungus spores in vitro, a toxic material was formed which caused inflammatory skin reactions in normal (noninfected, nonhypersensitive) guinea pigs.

To the best of our knowledge, the above summary mentions the most important types of skin reactions to trichophytin which have been heretofore observed and also includes the only types of antibodies which have been demonstrated in tinea infections.

Although urticarial or immediate wheal reactions have been shown to exist to extracts of nonparasitic (nonpathogenic) fungi (Storm von Leeuwen,[7] Hopkins, et al.), we know of no report of this type of reaction to extracts of pathogenic hyphomycetes or trichophytin. Furthermore, there exists no demonstration of Prausnitz-Küstner antibodies, that is, antibodies permitting the passive transfer of hypersensitiveness to trichophytin, although such passive transfer of hypersensitiveness to trichophytin has been reported by some of the above-mentioned authors in urticarial hypersensitiveness to air moulds.

On account of their theoretical interest, and because of possible importance in practice, the following experiments are reported.

EXPERIMENT 1.—L. S., a young man, suffered for several years from tinea of the hands and feet (epidermophytosis and epidermophytid). The clinical picture was classic. While fungi were demonstrated microscopically in the scales from the interdigital spaces of the feet, none could be found in the hand lesions.

An intradermal trichophytin injection (0.1 cm.) was given, and it was observed that the original (mechanical) wheal of approximately 0.5 centimeters diameter grew within 15 minutes to from 5.0 to 6.0 centimeters, was distinctly anemic and presented pseudopods and an angry, red areola.

Fig. 1.—Passive transfer of urticarial trichophytin hypersensitiveness. Photograph of back of normal nonhypersensitive individual.

The four areas at the left had been intradermally injected with 0.1 c.c. of serum of patient L. S. containing antibodies to trichophytin.

The four areas at right received deposits of normal serum.

After forty-eight hours the sites were scratched, and the uppermost on each side received an application of culture medium etc. (empty trichophytin),—no reaction.

The three lower sites on each side received applications of trichophytin, at left strongly positive reaction; at right (control), no reaction.

Intradermal injection with an "empty" trichophytin (that is, a liquid consisting of culture medium and preservative [phenol], but in which no fungi had grown), proved negative, the wheal becoming only slightly larger than the original traumatic elevation. Fourfold repetition of these experiments led to identical results.

In addition to the urticarial hypersensitiveness there was a typical late hypersensitive reaction to trichophytin to be observed after forty-

eight hours. This consisted in the appearance of the usual inflammatory papule and edematous zone.

As far as could be elicited from the not very intelligent patient, he had never suffered from urticaria, asthma, or hay fever. It is not to be assumed that he had had prior injections of trichophytin, as he stated that he had had none, and trichophytin has had but little employment in this country.

Conclusion.—A case of marked immediate urticarial hypersensitiveness to trichophytin is reported; the hypersensitiveness was directed to some substance or substances emanating from the pathogenic fungi, as tests with the culture medium and preservative alone did not cause a growing wheal. Although occurring in a case of ringworm infection, the question of the connection of this infection and the hypersensitiveness must be left open. Co-existent with the urticarial hypersensitiveness, the usual type of late inflammatory reaction to trichophytin was present.

EXPERIMENT 2.—In this experiment we attempted the passive transfer of the urticarial hypersensitiveness to trichophytin. The blood sera of L. S. (the patient with urticarial hypersensitiveness), and of patients with no urticarial hypersensitiveness, were injected intradermally in the skin of nonhypersensitive controls. The passive transference of the urticarial hypersensitiveness was successful in five successive cases. Both the purchasable trichophytin of Hoechst (Metz and Co.) and the trichophytin kindly lent to us by Werner Jadassohn, Chief of Clinic in the Dermatological Institute of Professor Bloch of Zürich, produced a wheal and erythema at the passively sensitized sites. The application of "empty" trichophytin called forth no such reaction.

Other sensitized sites were tested for us by Dr. M. Ramirez, by the application of extracts of several nonpathogenic fungi.

Saline extracts of: white penicillium, penicillium glaucum, mucor rhizopus, aspergillus glaucum were applied to sites containing the deposit of the serum of the tricophytin hypersensitive patient. With the exception of one case in which a wheal followed the application of penicillium glaucum,* all the tests with nonpathogenic fungi were negative. The mould extracts used were active, as demonstrated by the wheal formation in other individuals hypersensitive to the fungi in question. In no case did the control sites (that is, sites in which serum from patients without urticarial trichophytin hypersensitiveness had been deposited) show wheals or erythema.

CONCLUSION

The urticarial hypersensitiveness to trichophytin can be passively transferred by the method of Prausnitz-Küstner. There are circulating

*We can offer no explanation for this exception, but do not think it can be considered simply as a "group reaction."

antibodies in the blood serum which are the carriers of the hypersensitiveness, and which can passively sensitize the cells of the skin of normal non-sensitive individuals.

The antibodies seem to be specific; at least in our case they reacted only with trichophytin (one exception—penicillium glaucum) and not with the culture medium or with four nonpathogenic air moulds.

DISCUSSION

We wish here to discuss only the practical side of these observations. The discovery of the urticarial reaction to trichophytin, and of Prausnitz-Küstner antibodies to this substance, makes it possible that products of pathogenic hyphomycetes may be the causes of certain cases of urticarias, asthmas, and hay fevers. For it is in these conditions that urticarial skin hypersensitiveness and Prausnitz-Küstner antibodies have been found to exist.

Future experiments and investigation will show how frequently or rarely the tinea infection of the feet plays an etiologic rôle in the allergic diseases of the respiratory tract, and in urticarias and in the other allergic conditions. It is at least evident that opportunity for contact with the trichophytic allergen must be exceedingly frequent, almost universal, due to the prevalence of foot ringworm (''athlete's foot'') in this country.

In view of these facts, it seems to us essential that scratch skin tests with trichophytin be made part of the routine investigation of all asthmas, hay fevers, and urticarias of unknown etiology. For purposes of tests, the standard purchasable Hoechst trichophytin (imported by Metz and Co., New York City) seems adequate.

Dr. M. Ramirez, who has commenced testing some of his asthma patients with Hoechst trichophytin, is kind enough to permit us to state here that he has already had several cases with urticarial hypersensitiveness and demonstrable Prausnitz-Küstner antibodies, and one case in which a systemic reaction (asthma) followed the intradermal administration of trichophytin.[9]

The discussion of the theoretical importance of Prausnitz-Küstner antibodies to trichophytin, must be reserved until the results of further experiments with these antibodies are available.

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THE HEART IN BRONCHIAL ASTHMA*

An Electrocardiographic Study of 74 Cases

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FOR many years there has been a controversy regarding the heart in bronchial asthma. Much has been written on the subject, some claiming that the heart is not damaged even in long-standing asthma; others say the heart does become affected.

Most of the literature bearing on the subject is based on bedside work and is purely clinical. Many eminent men have contributed, some on one side, others opposing. Thus, Andral[1] in 1839 announced that "Asthma is a brevet of long life" and this view holds with many to this day. Walker[2] states that "although the elasticity of the lung in an asthmatic after a time becomes impaired and this makes the prognosis more unfavorable, integrity of the myocardium is rarely weakened."

On the other hand we have clinical evidence for the view that the heart is damaged in bronchial asthma. Bishop and Nelson[3] assert that "the chronic asthmatic has a large distended heart, particularly involving the right ventricle, the heart sounds are weak, and frequently tachycardia is present. The myocardium itself is at fault and, therefore, valvular murmurs are not common. The electrocardiogram usually shows a right predominance and low voltage."

Jagic[4] believes that long-continued asthma causes chronic pulmonary emphysema and this gradually brings on hypertrophy of the right section of the heart, as shown by physical and x-ray examinations.

Relatively few postmortems have been made in cases of bronchial asthma and reports here also are conflicting as regards the heart. For example, Kountz and Alexander[5] made three postmortem examinations; two patients had had long-standing asthma and in both, the hearts seemed normal. Alexander[6] reports ten autopsies in uncomplicated bronchial asthma; of these six were normal, two showed right ventricular hypertrophy, and two right ventricular dilatation. Wright[7] recently reported an autopsy with apparently normal heart in a woman who had had bronchial asthma for seven years. Lewis[8] does not believe that physical examination can differentiate left from right ventricular hypertrophy; he thinks that even inspection of the exposed

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Read before the Eighth Annual Meeting of the Association for the Study of Allergy, Detroit, June 23, 1930.

TABLE I

NO.	SEX	AGE YEARS	DURATION	FAMILY HISTORY	ASSOC. ALLERGY	SKIN TESTS	EOSIN.	B. P.	PULSE	ELECTROCARDIOGRAM
1	M	55	20	0	0	Pos.	3	130/80	70	Normal
2	M	5	5	Pos.	?	0	3	------	--	Low R_1, High R_3
3	F	34	10	Pos.	0	0	2	136/92	80	Normal
4	F	25	8	Pos.	Pos.	Pos.	0	------	106	Low R_1, High R_3
5	M	53	18	?	0	Pos.	5	120/80	76	L.A.D.
6	F	16	13	Pos.	0	Pos.	0	------	100	Normal
7	M	7	7	Pos.	Pos.	Pos.	6	------	100	L.A.D.
8	M	10	6	Pos.	0	Pos.	4	------	90	Normal
9	M	43	7	0	0	Pos.	0	114/80	80	Mild conduct. disturb.
10	F	5	1	0	0	Pos.	8	------	--	Normal
11	M	38	25	0	Pos.	Pos.	2	106/70	88	Low R_1, High R_3
12	M	53	6	0	Pos.	Pos.	–	114/76	84	Normal
13	M	48	1	0	0	Pos.	5	120/80	86	L.A.D., conduct. disturb.
14	M	35	11	0	0	Pos.	–	134/80	90	Normal
15	M	37	6	0	0	Pos.	3	118/90	84	Normal
16	M	42	3	0	0	Pos.	5	145/80	100	Normal
17	M	10	2	Pos.	0	0	0	------	--	Normal
18	F	25	1	?	0	Pos.	14	110/70	120	Low R_1, High R_3
19	F	32	1	Pos.	0	0	3	130/90	92	L.A.D.
20	M	7	2	0	0	Pos.	2	------	--	Low R_1, High R_3
21	M	23	2	0	0	Pos.	0	128/96	92	R.V.P., conduct. disturb.
22	F	24	12	0	0	Pos.	–	100/70	80	Low R_1, High R_3, cond. disturb.
23	M	41	2	Pos.	Pos.	Pos.	–	120/86	96	Low R_1, High R_3, cond. disturb.
24	M	5	4	Pos.	0	–	2	------	98	Low R_1, High R_3
25	F	32	3	0	0	?	–	110/70	64	Low R_1, High R_3
26	M	58	2	0	0	0	1	100/75	104	Low R_1, High R_3
27	M	12	6	0	Pos.	Pos.	11	------	88	Low R_1, High R_3
28	M	36	36	0	Pos.	Pos.	2	120/80	76	R.V.P.
29	F	39	5	0	Pos.	Pos.	–	120/78	76	Normal
30	M	51	6	0	Pos.	Pos.	3	106/80	78	Normal
31	M	52	3	0	0	0	–	132/84	80	Normal
32	M	30	6	Pos.	Pos.	Pos.	6	------	88	Low R_1, High R_3
33	F	12	11	Pos.	Pos.	Pos.	5	96/70	102	Low R_1, High R_3
34	M	23	2	0	0	Pos.	4	120/80	88	Normal
35	M	10	5	0	0	0	2	------	--	Low R_1, High R_3
36	M	16	8	0	0	Pos.	10	115/78	80	Low R_1, High R_3, cond. disturb.
37	M	43	15	0	0	Pos.	8	--	80	Normal

TABLE I—CONT'D

NO.	SEX	AGE YEARS	DURATION	FAMILY HISTORY	ASSOC. ALLERGY	SKIN TESTS	EOSIN.	B. P.	PULSE	ELECTROCARDIOGRAM
38	F	51	9	0	0	Pos.	3	140/90	76	L.A.D., slight cond. disturb.
39	M	39	1	0	?	Pos.	0	148/90	94	Low R_1, High R_3
40	M	7	½	0	0	Pos.	13	------	--	Low R_1, High R_3
41	F	22	2	0	Pos.	Pos.	5	120/80	100	L.A.D.
42	F	21	1	0	0	0	–	116/76	90	Low R_1, High R_3
43	M	34	1	0	Pos.	Pos.	6	130/80	72	Normal
44	F	7	5	0	0	Pos.	3	------	--	Low R_1, High R_3
45	F	34	4	0	0	–	5	124/70	100	Low R_1, High R_3
46	M	9	4	0	Pos.	Pos.	0	------	--	Normal
47	M	49	10	?	0	0	6	------	64	Low R_1, High R_3
48	F	44	9	0	0	0	7	135/70	92	R.A.D., cond. disturb.
49	F	50	3	Pos.	0	Pos.	0	140/85	100	Moderate cond. disturb.
50	F	19	2	0	0	Pos.	2	100/50	72	R.A.D.
51	F	40	4	0	0	0	0	160/100	100	Normal
52	F	44	1	0	Pos.	Pos.	0	120/76	86	L.A.D.
53	M	42	12	Pos.	0	Pos.	2	124/80	80	Cond. disturb.
54	F	24	1	0	Pos.	Pos.	11	96/62	88	Low R_1, High R_3
55	M	32	1	0	Pos.	Pos.	6	120/90	90	Normal
56	M	41	4	0	Pos.	0	8	98/58	72	Low R_1, High R_3
57	F	11	7	0	Pos.	Pos.	2	------	--	Low R_1, High R_3
58	M	22	1 mo.	0	0	Pos.	0	140/90	88	Low R_1, High R_3
59	F	21	15	Pos.	0	Pos.	6	132/78	80	Low R_1, High R_3
60	F	8	5	Pos.	0	Pos.	3	------	--	Normal
61	F	31	8 mo.	0	0	0	6	100/70	104	Cond. disturb.
62	M	5	3	0	Pos.	Pos.	5	------	--	Normal
63	M	9	7	0	0	Pos.	1	------	--	Low R_1, High R_3
64	F	22	5	Pos.	Pos.	Pos.	12	120/74	76	Low R_1, High R_3, cond. disturb.
65	M	4	1	Pos.	0	Pos.	21	------	--	Low R_1, High R_3
66	F	32	13	–	Pos.	Pos.	4	140/90	92	Mild cond. disturb.
67	F	38	2	0	0	Pos.	0	------	84	Low R_1, High R_3
68	F	33	3	0	Pos.	Pos.	0	110/77	78	Low R_1, High R_3
69	F	10	3	Pos.	Pos.	Pos.	0	------	--	Low R_1, High R_3, cond. disturb.
70	M	10	7	0	0	Pos.	0	------	--	Low R_1, High R_3
71	F	24	9	0	0	Pos.	2	------	96	Low R_1, High R_3
72	M	10	8	Pos.	Pos.	Pos.	6	------	--	Normal
73	M	32	27	0	Pos.	Pos.	7	120/78	72	Low R_1, High R_3
74	M	5	1	Pos.	Pos.	Pos.	0	------	--	Normal

heart is quite insufficient in studying hypertrophy; a method of weighing the muscles of the separate chambers is alone reliable.

With controversies at the bedside and even at the postmortem table we are fortunate in being able to attack the problem by another method, electrocardiogram. To date only two important investigations have appeared along this line and these do not agree at all.

Alexander, Luten, and Kountz[9] studied fifty patients with bronchial asthma in whom the disease was of long standing, an average of over ten years, and found that the heart remained singularly free from damage, despite the fact that emphysema was present in all but one. Only three showed cardiac damage, but in two of these cases the cardiac disease preceded the asthma and the third patient was seventy-eight years old and had fibrillation. Excluding these three which probably should not have been included in the series they find 100 per cent normal hearts in these long-standing cases of asthma. Their work seems to have been done quite carefully and all the cases were diagnosed true bronchial asthma.

The opposing paper is by M. H. Kahn[10] who also studied fifty cases. Kahn quotes Einthoven, Miller, Lewis and Quilder, and others to show that the electrocardiogram accurately records preponderance of one or the other ventricle, and that this may be taken as an index of relative hypertrophy. In his cases he found 19 normals, 10 right ventricular preponderances, 21 left ventricular preponderances, 10 T_3 inverted. Those with left ventricular preponderance had associated hypertension and most of these were over forty years of age (18 of 21). He found right ventricular preponderance in the young, especially (7 of 10 under thirty years), and concludes (1) that 20 per cent showed electrocardiographic evidence of right ventricular preponderance and (2) that the rest showed equal numbers of no preponderance or left ventricular preponderance. Many of these cases had hypertension and aortic atheromas, factors sufficient to cause such hypertrophy of the left ventricle as to mask the electrocardiographic evidence of right ventricular preponderance. (3) Four cases with right ventricular preponderance also had high P_2 and P_3. (4) Inversion T-wave in Lead III showed no particular relation to the ventricular preponderance.

Kahn's work is open to criticism because (1) x-ray examinations were not made, (2) he did not publish criteria by which the diagnosis of bronchial asthma was made, and (3) he included cases of high blood pressure; this accounts for many of his left ventricular preponderances. However, many of Kahn's cases must have been true bronchial asthma, and the fact that he found 20 per cent with right ventricular preponderance cannot be thrown aside.

Our study has been made on clinic cases and we have tried to be as thorough and as careful as possible. The cases were taken in order without any selection except that all were diagnosed true bronchial

asthma. This was done by the usual history, complete physical examination, thorough skin testing, chest x-rays, sputum, blood counts, and Wassermann tests.

To offset the argument against Kahn's work we excluded all doubtful cases. Thus we left out all cases of high blood pressure and all with cardiac histories (edema, etc.), or who had definite clinical evidence of myocardial degeneration as shown by large hearts with hypertension, angina pectoris, etc. When we were in doubt as to the possibility of cardiac asthma being present instead of bronchial asthma, we omitted the case from the group.

There were left 74 cases of true bronchial asthma and Tables I, II, and III reveal our findings: of these 43 were males, 31 females. A definite family history of allergy was present in 21 and doubtful in 3, other allergic diseases were present in 27, doubtful in 2. Positive skin tests were obtained in 58 cases or 78 per cent. Eosinophile counts were done in most cases, but did not help much.

Table I shows the 74 cases in detail along with the electrocardiographic findings. Table II summarizes these findings and groups the cases according to age. The results are as follows: (1) only 23 of 74 gave perfectly normal electrocardiograms, (2) 35 showed a low R in Lead I and a high R in Lead III; this is considered by competent electrocardiologists to indicate a tendency toward right axis deviation, certainly not normal. (3) Four additional cases gave frank right axis deviation or right ventricular preponderance. (4) Seven showed left axis deviation, indicating left heart strain. (5) Fourteen cases revealed mild conduction disturbances. (6) Some of the cases showed two changes, such as conduction disturbance plus low R_1, and high R_3.

TABLE II

AGE IN YEARS	1-9	10-19	20-29	30-39	40-49	50-59	TOTAL	PER CENT
Normal	5	4	1	6	3	4	23	31.0
Low R_1, High R_3	7	7	9	8	3	1	35	47.3
R.A.D.	0	1	0	0	1	0	2	2.7
R.V.P.	0	0	1	1	0	0	2	2.7
L.A.D.	1	0	1	1	2	2	7	9.4
Conduction Disturbance	0	2	3	2	5	2	14	18.9
Total Cases	13	14	15	18	14	9	83	---

Table III shows the duration of the asthma in the cases with low R_1 and high R_3, 28 of 35 had asthma from one to ten years; two showed

TABLE III

DURATION OF ASTHMA OF CASES WITH LOW R_1 AND HIGH R_3	
Less than 1 year	2 (5.7%)
1 to 5 years	19 (54.3%)
6 to 10 years	9 (25.7%)
11 to 20 years	3 (8.5%)
21 to 30 years	2 (5.7%)

this tendency toward right axis deviation in less than one year of symptoms.

All of these patients had regular heart rates with no murmurs, no enlargement, and no definite cardiac symptoms or findings.

COMMENT

It is evident from this series that there is a definite damage or tendency toward damage to the heart in bronchial asthma. The small percentage of perfectly normal tracings should make us try all the harder to see these cases early, before the complicating emphysema and bronchitis come on and before the heart is damaged.

SUMMARY

1. The diagnosis of true bronchial asthma was made in 74 cases by careful history, examination, blood count, Wassermann, sputum, thorough skin tests, and chest x-rays.

2. All doubtful cases, e.g., hypertension, decompensation, etc., were excluded.

3. Electrocardiograms demonstrated that the heart is damaged or tends to be damaged in a majority of all cases. Only 23 (31 per cent) were normal.

4. The striking finding is the great frequency of a low R_1 and high R_3; this must be considered as strongly suggesting that the heart is on its way toward right axis deviation due to right heart strain.

I am greatly indebted to Dr. C. C. Maher of the Cardiac Clinic for most valuable aid in reading and interpreting the electrocardiograms.

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THE VARIABILITY OF SKIN REACTIONS IN ALLERGY*†

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THE development of the skin test for "protein sensitization" was largely responsible for the clinical appreciation of allergy. This was due to the conception that the test would reveal, not only the particular protein (allergen) to which the body may be hypersensitive, but also the degree of sensitivity present. In this country the skin test became extensively used, but in recent years its dependability has been questioned. Although its value is admittedly great when positive reactions occur and are correctly interpreted, yet its failure to respond in cases of obvious allergy is discouraging its general use to a considerable extent.

Those who have had much experience in applying the skin test recognize the inconstancy of positive reactions in patients with hypersensitiveness. For instance, reactions are the rule in hay fever and juvenile eczema and are infrequent in urticaria. They are much more common in the first two decades of life than the later ones. Although there is some speculation concerning the factors underlying these discrepancies, there is no accepted proof that explains them.

Of considerable interest is another type of variability of allergic skin reactions. This occurs in hypersensitive individuals in whom a positive response is obtained, but is one which varies in intensity at different sites on the skin. A study of this irregularity has led to a consideration of the underlying factors that enter into wheal formation, as this is the essential lesion by which the positive allergic skin test is identified. The present paper is an introduction to this study.

The wheal of a positive skin reaction is a circumscribed swelling surrounded by a red aureolar zone (the flare). When sectioned, the wheal shows an intense edema containing more or less round cells and eosinophiles, the amount of which depends on its duration when excised. Such an edema is the principal anatomic lesion of allergy.[1] These sections from the skin are essentially similar to those from the nose,[2] the bronchi,[3, 4] and the bowel,[5] when taken during acute allergic reactions. The positive skin reaction thus represents a typical allergic lesion, and any information revealed which concerns its formation should apply to allergic edemas elsewhere.

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†Read in abstract form before the Sixth Annual Meeting of The Society for the Study of Asthma and Allied Conditions, Atlantic City, N. J., May 3, 1930.

Excepting the presence of eosinophiles, a precisely similar edema may be induced by the introduction of a suitable histamine solution into the skin. It has been determined[6, 7] that what actually takes place when such whealing occurs, is a capillary dilatation about the site of the introduction of allergen and a transudation of blood plasma (and cells) into the tissue spaces. The capillary response to the stimulus involved is a direct one. The flare, on the other hand, involves a widening of the surrounding arterioles and is a local reflex.

There is some difference of opinion concerning the immunologic mechanism involved in this process. Evidently the injected allergen comes in contact with some substance in the skin (antibody) with which it reacts specifically. As a result of this contact, it is presumed that a physical or physicochemical agent which acts directly on the capillaries is liberated. These capillaries then dilate and become permeable to their contained plasma, and an edema results. This theory has been considered by Lewis[7] in his recent studies on the skin capillaries. Lewis believes the chemical agent released on contact of antigen with the skin cells to be histamine or something akin to histamine which he calls "H-substance." He proposes an alternate theory of the mechanism of allergic response which is based on the action of the allergen directly on the capillary mechanism without the mediation of skin tissue. Van Leeuwen[8] is in agreement with this latter view. Lewis concludes, however, that a fundamental factor in the anaphylactic (allergic) reaction is the liberation of H-substance. To generalize this theory it may be stated thus: Injected allergen comes in contact with a specific substance in skin tissue (antibody) with the resultant formation of H-substance. H-substance acts immediately and directly on the capillaries and an edema results.

Applying these factors clinically, one finds that they require further analysis. This is based on the fact that when a specific allergen is applied to different sites of the skin of a given hypersensitive individual, there is a great variability in the degree of local reaction. This was pointed out in a preliminary report.[9] It was demonstrated as follows:

Patients with hay fever were selected because positive skin reactions are quite constantly present in these individuals. Two one hundredths c.c. of a 1 to 1,000 dilution of the specific pollen extract was injected intradermally at four well separated sites. Duplicate injections were made in each instance. Unless each pair of resulting wheals approximated each other in size, the test was discarded because of the likelihood of a break in the technic of injection. A blue-barrel Luer syringe of 1.0 c.c. capacity was used to which a second barrel with graduations marked in 0.01 c.c. was attached. These markings are

spaced at sufficiently wide intervals to insure quite accurate measurement of the injected fluid.

The skin of the upper anterior forearm, of the back, the abdomen and outer leg, was injected in order, and the time was taken at the completion of each pair of injections at these sites. Fifteen minutes after injection, the resulting wheals were outlined in ink. Planimeter measurements were made of the enclosed areas and recorded in square centimeters. Fifteen such patients were tested, and in twenty-one others the forearm, back and the upper and outer aspect of the thigh were injected. Although there were individual variations, it was found that the skin of the trunk gave consistently larger reactions

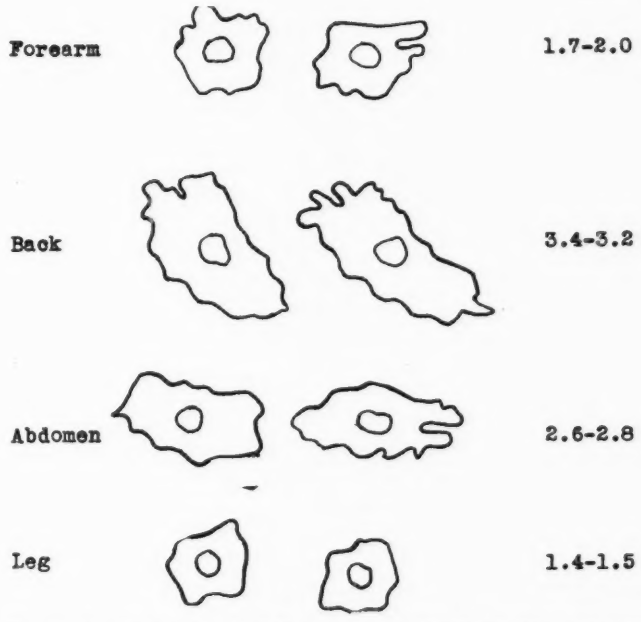

Fig. 1.—Ragweed pollen extract, 0.02 c.c. of a 1-10,000 dilution, injected into various sites of the skin of a hay fever patient. Figures give area of wheals measured in square centimeters fifteen minutes after injection.

than that of the extremities. The reactions on the thigh were usually greater than those on the leg or forearm (Fig. 1).

In such a test as this, many errors may occur. The amount of fluid injected is, of course, important, but this is quite well controlled by the attachment affixed to the syringe. The depth of injection is, perhaps, the most difficult step to control. This can only be estimated and consistent results come from practice. The fact, however, that two wheals of approximately the same size were obtained at each site in the cases reported, as well as the great variation in the size of the wheals that occurred in different regions of the skin, minimizes the technical errors of injection. Another factor that is not at all ac-

counted for is the third dimension of the wheal, namely, its vertical diameter. This, however, is not considered of much consequence, for after the initial rise the spread is far greater laterally into normal tissue that vertically into distended skin.

The size of a skin wheal may be dependent on various factors, as Lewis has pointed out. Interference with blood supply by a tourniquet, holding the part (arm) erect, the texture of the skin (looseness or thickness), also differences in distribution of vascular (capillary) supply and of lymphatic architecture, and doubtless other factors, such as those which may influence histamine formation, may affect whealing. Consequently, any comparison of the size of wheals on various sites of the skin must take such factors into account. These are being studied, but as yet there is no evidence which indicates that they are important, other than the possible differences in thickness of the true skin,* and also certain factors which may modify the action of histamine.

As stated above, a conception of the immunologic mechanism which controls the formation of a positive skin reaction, presupposes that the injected allergen comes in contact with antibody in the skin tissue. As a result, a capillary dilating substance is liberated. In view of the finding that positive reactions are smaller at some sites of the skin than at others, certain possibilities in terms of this conception present themselves to account for the smaller wheals. Inasmuch as the amount of injected allergen has been kept constant there may be: (1) an irregular distribution of antibody in the skin; (2) the failure of allergen and antibody to react uniformly at different sites, with a resultant variation in the amount of dilating substance (H-substance); (3) an inherent difference in response to H-substance on the part of the capillaries of different regions of the skin.

The possibility of an irregular distribution of antibody throughout the skin was studied. Advantage was taken of the fact that a histamine wheal is essentially identical to that of a positive allergic skin reaction. Nonallergic subjects were selected, and the effect of histamine response on normal skin was determined. Immunologic factors were thereby eliminated.

*Lewis and Grant[10] in one of their early papers pointed out that histamine wheals varied in size at different sites of the skin. They showed this by stroking the forearm and observed a diminution of intensity of the stroke as it ran distally. At the same time they laid a row of histamine wheals parallel to the stroke and likewise noted a gradual decrease in the size of these proportionate to the decrease in intensity of the stroke. These authors suggested that this variation is due in large part, if not wholly, to a varying thickness of the true skin. It is not clear why thicker skin should give a different reaction than thin skin, unless in the former there may be more capillaries or more opportunity for elaboration of H-substance. Since this H-substance and histamine to which they compare it presumably have the same effect on the capillaries, it is difficult to see why histamine applied directly to the capillaries of thin skin should give less a reaction than when applied to thick skin. One must presume that histamine acts as other irritants do through the mediation of H-substance, or that the product of the two is more in thick skin than in thin skin. Their point is not clear.

A series of twenty-one normal subjects were injected intradermally with 0.02 c.c. of a 1 to 2,000 dilution of histamine phosphate (Pfanstiehl). The injections were made in the intrascapular region, in the forearm and the upper outer aspect of the opposite thigh. At each site, two injections were made, and unless the two wheals of each pair approximated each other in size, the test was discarded because of faulty technic. A Luer tuberculin syringe with an attachment for more accurate measurement described above was used. After each pair of wheals had developed for fifteen minutes, they were outlined in ink, and these marks were copied on tracing paper. Planimeter measurements were made of the enclosed areas and recorded in square centimeters.

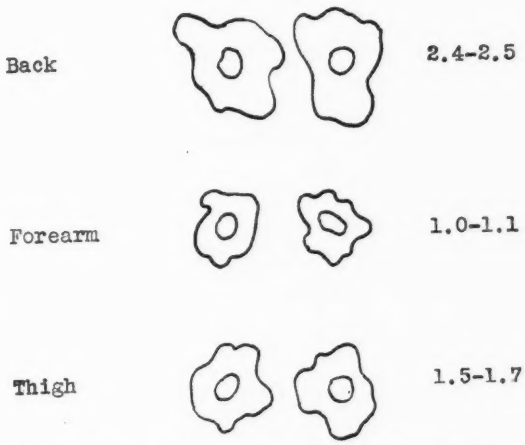

Fig. 2.—Histamine acid phosphate, 0.02 c.c. of a 1-2,000 dilution, injected into various sites of the skin of a normal subject. Figures give area of wheals measured in square centimeters fifteen minutes after injection.

It was found that there was a distinct variation in the size of wheals obtained at various sites. (Fig. 2.) Those on the trunk were larger than those on the forearm, whereas wheals on the thigh were intermediate between the two. Table I shows a series of these measurements. Similar measurements were made in a group of allergic subjects in whom specific allergens were injected. (Table II.) In averaging the size of the resulting wheals in both series, there happens to be an approximation between the two. This, of course, is a matter of chance and could be changed entirely by varying the strength either of the allergen or of the histamine. Of significance, however, is the ratio to one another of the average size of wheals obtained at the three sites: With histamine it is, forearm 0.26; back 0.40; thigh 0.34. With allergens it is, forearm 0.24; back 0.45; thigh 0.31.

Similar tests were carried out in allergic patients who received both specific allergens and histamine. Here, two wheals with each sub-

TABLE I

DUPLICATE PLANIMETER MEASUREMENTS OF WHEALS INDUCED BY 0.02 C.C. OF A 1 TO 2000 DILUTION OF HISTAMINE PHOSPHATE, FIFTEEN MINUTES AFTER INTRADERMAL INJECTION. RESULTS RECORDED IN SQUARE CENTIMETERS

FOREARM		BACK		THIGH	
1.0	1.1	2.0	2.0	1.5	1.4
1.4	1.2	2.3	2.5	1.7	1.7
1.6	1.5	2.3	2.5	1.8	2.0
1.5	1.4	2.2	2.3	2.0	1.8
1.5	1.4	2.0	2.2	1.7	1.8
1.5	1.5	2.7	2.5	2.0	1.7
1.3	1.3	1.3	1.9	1.5	1.6
1.2	1.2	2.2	2.2	1.4	1.5
1.6	1.5	2.4	2.2	2.0	2.3
1.4	1.5	2.1	2.6	1.7	1.6
1.2	1.4	1.9	1.6	2.3	2.0
1.0	0.9	2.4	2.0	1.5	1.4
1.6	1.7	1.7	1.6	1.5	1.4
1.4	1.5	1.0	1.0	1.7	1.7
1.1	1.0	1.4	1.7	2.1	1.6
1.4	1.3	2.7	2.1	1.7	1.7
1.3	1.3	2.0	1.8	1.9	1.9
1.0	1.4	2.0	1.7	1.8	1.7
2.0	1.4	1.7	1.4	1.5	1.3
1.0	1.4	2.0	2.3	2.1	2.1
1.2	1.1	2.5	2.6	1.3	1.4
Average = 1.35		Average = 2.03		Average = 1.74	
Ratio 0.26		: 0.40		: 0.34	

TABLE II

DUPLICATE MEASUREMENTS OF WHEALS INDUCED BY 0.02 C.C. OF ALLERGEN EXTRACTS IN HYPERSENSITIVE INDIVIDUALS, FIFTEEN MINUTES AFTER INTRADERMAL INJECTIONS. RESULTS RECORDED IN SQUARE CENTIMETERS

FOREARM		BACK		THIGH	
1.1	1.5	2.0	1.5	2.0	1.1
.6	.7	.9	1.0	1.7	1.5
.7	.5	1.0	1.1	1.7	0.7
.9	1.0	2.5	2.0	1.1	2.6
1.2	1.1	2.4	2.5	1.5	1.6
2.0	1.9	3.7	3.1	.7	.6
1.5	1.0	1.4	1.1	1.6	1.4
.6	.6	2.2	2.4	1.1	1.2
1.2	1.4	1.0	2.2	1.8	1.5
1.8	2.0	2.6	3.4	2.6	2.6
1.5	1.7	2.5	3.2	1.7	1.4
2.1	1.7	3.4	3.3	1.5	1.6
1.8	1.6	3.7	4.1	2.2	2.3
.8	.9	2.4	2.0	1.0	1.2
Average = 1.22		Average = 2.27		Average = 1.57	
Ratio 0.24		: 0.45		: 0.31	

stance were induced at the three sites. It has been shown that such skins are no more sensitive to histamine than is normal skin. The same correspondence in ratio was noted, although in several subjects the variations in size were somewhat more with allergens. One such experiment is shown in Fig. 3. Here it so happened that the strength of the histamine and that of the allergen were such that all four wheals at each site approximated one another in size.

A few tests were carried out with atropine sulphate and codeine phosphate on normal skins. These substances also cause whealing, and the variations in size after injections of constant amounts into the three sites were comparable to the results obtained with allergens and with histamine. It is noteworthy that Gröbel[11] recently performed similar intradermal tests with morphine in nine normal children and one adult. He injected each at thirteen sites and found also that, by

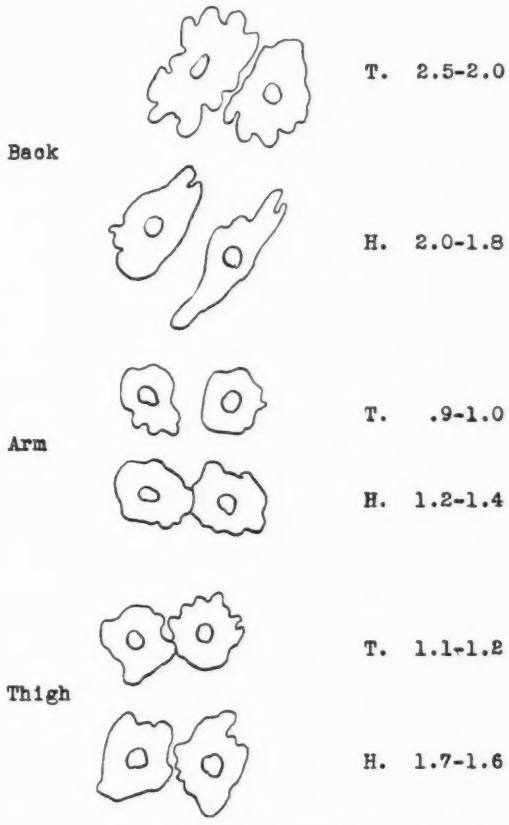

Fig. 3.—T = 0.02 c.c. of 1-10,000 timothy extract; H = 0.02 c.c. of 1-2,000 histamine acid phosphate. Figures give area of wheals measured in square centimeters fifteen minutes after injection.

and large, the skin of the trunk gave larger reactions than that of the extremities.

The close similarity in appearance, time of development and variation in size between wheals induced by allergens and by histamine would permit the assumption that similar factors are concerned in the development of each. Whatever it may be that causes a difference in the size of wheals induced by constant amounts of histamine at various sites of the skin, should hold true also for allergens.

Inasmuch, therefore, as the variability of skin reactions in allergy is evidently not due to an irregular distribution of antibody in the skin, there remain the possibilities of a faulty liberation of H-substance as a result of contact between allergen and antibody, and also an inherent difference of response to H-substance on the part of the capillaries.

The first assumption cannot be ruled out in the above experiments. According to Lewis, H-substance and histamine are essentially identical. Although it would appear that the deliberate injection of histamine should eliminate any consideration of a variability of a capillary dilating substance, yet this is not necessarily the case. The possibility that histamine itself may release further H-substance in the skin tissue must be considered, but this would imply that certain portions of the skin contain more H-substance than others. This is suggested by the chemical analysis of skin tissue by Harris,[12] who was able to extract more histamine from the skin of the chest and prepuce than from that of the thigh or breast. Although such experiments are suggestive, they by no means imply either that histamine releases H-substance or that more H-substance can be released from one site than from another. A more likely explanation depends on the fact that the whealing action of histamine may be enhanced by certain salts such as phosphates and salts of calcium.* This possibility can by no means be excluded, and is being studied.

There is little to substantiate the hypothesis that there is an inherent difference of response to dilating substances on the part of the capillaries of various portions of the skin. In order to examine this possibility, however, the following experiments were made.

Advantage was taken of the fact that histamine wheals in dog's skin are apparently identical to those of human skin. Török and Lehner[13] found them to be histologically alike, and we confirmed this observation. Their time of appearance after injection, their size and shape are quite like those in normal human skin. Moreover, there is the same variability in the size of response to histamine wheals at various sites in a dog's skin. Wheals on the abdomen are larger than those on the thigh, which in turn exceed those on the leg. This was pointed out many years ago by Török and Hari.[14]

Accordingly, having determined that a larger response to 0.02 c.c. of a 1 to 1,000 histamine phosphate solution was obtained on the shaved skin of the outer aspect of the thigh of a dog than on the outer leg, perfusion experiments were done. The perfusate was dog's blood to which sufficient histamine phosphate was added to give a concentration of 1 to 1,000 of this drug. A blood pump was used and the perfusate aerated with an O_2 (95 per cent) CO_2 (5 per cent) mixture.

*To be published.

It was difficult to tie off sufficient collateral vessels to make the leg bloodless. It was noted, however, that the entire extremity below the point of perfusion turned a uniform pink. This indicated that with histamine introduced in this way there seemed to be no difference in response between the capillaries of the thigh and those of the leg. When this concentration of histamine was injected into the intact femoral artery, the same diffuse blush over the entire extremity occurred. It is interesting that at no time was wheal formation noted. Doubtless a diffuse edema occurred, but no volume measurements were made. These experiments are in accord with those of Harmer and Harris,[15] who injected histamine into humans and noted a diffuse blushing of the skin.

From these experiments on dogs no conclusions can be drawn, for many errors enter into the method, and results from intravenous introduction of histamine cannot be compared to local application. However, the results may throw some doubt on the highly conjectural assumption that there is an inherent difference in the response of capillaries of various parts of the skin to the dilating effect of histamine.

DISCUSSION

The skin test in allergy, as a clinical measure of importance, shows a fallibility which demands precaution in its interpretation. Not only is it recognized that in some cases of clinical allergy a positive reaction is absent, but it is also evident that when it does appear, its intensity need by no means indicate the underlying degree of sensitivity. Consequently, the conventional signs of one plus, two plus, etc., should be modified by the designation as to what part of the skin the test was applied. A patient may give a plus minus reaction on the arm and a two plus or three plus reaction on the abdomen.

The variability of positive response on different sites of the skin has led to a consideration of the factors involved in the production of these reactions. It was found that differences in size of wheal formation observed in allergic subjects are essentially similar to those that occur with histamine in normal individuals. Inasmuch as the amounts of fluid injected were kept constant in each instance, it appears that the factors responsible for the variation in size of reaction reside in normal skin and therefore are not due to immunologic influences. To be sure, there is a quantitative relationship between the amount of allergen injected and the positive response elicited, but the fact that this is not constant everywhere on the skin in a given case implies that there is some mediating factor in the skin itself. In all probability this is to be found in the skin cells rather than in the capillaries. The subject of capillary permeability is most complicated and involves such forces as capillary blood pressure, filtration pressure, etc. Yet,

in so far as is known, the rôle of dilatation and permeability in local allergic reactions seems to be largely dependent upon the amount of dilating substance (H-substance) available; or rather upon those factors which would permit H-substance present to have an optimum effect upon the surrounding capillaries.

Since it would appear that there are certain influences residing in the skin cells which may modify the formation of local edema, it is quite conceivable that these influences may be responsible for the great variability of reaction which occurs in clinical allergy. In bronchial asthma, for instance, there is evidence that not all the bronchioles are affected at a given time, but only portions of the bronchial tree.[16, 17] The same has been found in gastrointestinal manifestations of food allergy.[18] The phenomenon is well exemplified in allergic urticaria due to foods. In this instance, although the skin cells are bathed with allergen in the blood stream, the variability of response is demonstrated by wheals of different size, numerous or few, with unaffected skin between. If one outlines in ink a crop of such wheals, it will be found the following day that the marked wheals will have disappeared and that new lesions will be found on skin previously unaffected. It seems conceivable that in such instances the variability is due to influences within the tissues which control the action of H-substance whether this term refers to capillary-dilating or bronchoconstricting action.

What the tissue factors may be that influence the action of H-substance is problematical. It is known, however, that the smooth muscle contracting action of histamine is inhibited by aldehydes[19] and its whealing action enhanced by certain salts (sodium phosphate, calcium sulphate) in given concentrations. As there is considerable evidence that ionic concentrations vary in different tissues and at different times, one may speculate how this could influence the action of H-substance. Experiments dealing with this phase of the subject, of which the present paper is an introduction, are being carried on.

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A CLINICAL STUDY OF THE USE OF CALCIUM IN CONTROLLED CASES OF ALLERGY*

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THE pharmacologic background for the use of calcium in allergy is found in the work of Howell,[1] who demonstrated that the effect of potassium and calcium on the cell is antagonistic; that there is a definite balance between the quantities of these two elements in the cell; that an increase either relative or absolute in the potassium ions results in an effect similar to that following parasympathetic or vagus stimulation, and that a calcium ion increase simulates the effect of sympathetic stimulation. Since the various allergic states are associated with symptoms of vagotonia, it has been assumed that there may be a calcium deficiency in these conditions with a resultant relative potassium ion increase and consequent overactivity of the vagus.

Pottenger[2] believes that the administration of calcium is of benefit. Similar views are held by Hoffman,[3] Goeppert,[4] Brown and Hunter,[5] and Novak and Hollander.[6, 7] The last mentioned authors reported that cases of hyperesthetic rhinitis had low blood calcium contents and reported a rise in the blood calcium following the administration of calcium lactate and thyroid extract by mouth. With the rise in blood calcium there was clinical improvement.

At the time of this report one of us (M. B. C.) repeated the work of Novak and Hollander with disappointing results. Our chemical studies did not reveal the calcium deficiencies which were described. In fact we found that the factors of error in the chemical methods then in use for the estimation of total blood calcium were sufficiently great to account for greater differences than those on which conclusions as to the presence of the deficiency were based. Since we found no conclusive evidence of deficiency in the total blood calcium we attempted to study the so-called ionic or diffusible calcium. Here the technical difficulties are such that variations as large as 25 per cent may occur on attempts to measure added calcium so that in our opinion no calcium deficiencies have been demonstrated regularly in any of the allergic states. Our clinical trials were also disappointing so that for several years we gave no calcium to any of our patients. Recently, however, we decided to restudy this problem clinically because we had under our care a

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Read before the Eighth Annual Meeting of the Association for the Study of Allergy, Detroit, June 24, 1930.

group of patients whom we had studied for one year and on whom all methods of treatment had been tried without modification of their symptoms. We felt that these patients enabled us to have a base line for comparison since we knew the vagaries of the disease in each, and that any definite improvement noted could be attributed honestly to the calcium administered.

Accordingly, ten such cases comprising those with urticaria, vasomotor rhinitis, and asthma were treated as follows: each patient was given sufficient Calcium Sandoz so that two teaspoonfuls could be taken daily for a period of one month. The powder was dissolved in water and was taken in two doses daily on an empty stomach. In addition, each patient received on alternate days either intramuscularly or intravenously a 10 c.c. ampoule of Calcium Sandoz in solution. At the end of the test period each patient had ingested at least 8 ounces of Calcium Sandoz and had been injected with 120 to 150 c.c. of the solution of Calcium Sandoz.

The results were very disappointing. In not a single instance was there any amelioration of the symptoms, either in the acute or chronic states. The case histories of these patients were all typical of allergy. Physical and x-ray examination as well as skin tests pointed toward allergy. The usual desensitizing and elimination methods were not very successful.

About the same time our work was going on Tainter and Van Deventer[8] of the Stanford School of Medicine were testing the antiedemic actions of calcium lactate under carefully controlled conditions. According to their results, the element is inert and useless in these states except as it may act at the expense of circulatory injury. These investigators state frankly that the alleged specific antiedemic action of calcium lacks a satisfactory experimental basis, and the theoretical antipermeability effect of calcium on tissues or organs in situ lacks convincing evidence.

Shortly after our work was finished, Ramirez[9] reported that he had not seen clinical improvement following the raising of the blood calcium in allergic patients. He did say, however, "I do not mean to imply that some cases have not shown temporary improvement. This is particularly true of urticaria, but the improvement does not last long and may have been caused by many other factors unrelated to calcium administration." In our series we have eliminated as far as possible extraneous factors so that we could attribute any change to the calcium administered.

We are thus forced to disagree with Pottenger, O. H. Brown, G. T. Brown, Sterling,[10] Novak and Hollander, and others and to conclude with Criep and McElroy[11] and Ramirez that calcium therapy is of little or no clinical value in allergy.

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10616 EUCLID AVENUE.

STUDIES IN ALLERGY*

II. A CASE OF SENSITIVENESS TO CUTTLEFISH BONE

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GLEN RIDGE, N. J.

THE importance of this paper lies wholly in the fact that it records a clinical reaction to a substance heretofore unrecognized.

CASE HISTORY.—T. H., male, age twenty-nine years, born in Turkey, was admitted to the clinic in March, 1930, with a history of bronchial asthma for five years. Six months prior to the onset of his trouble he obtained a position with a firm of jewelry manufacturers. Three months after his employment he developed a persistent dry cough and frequent attacks of a chest condition that was called bronchitis. The condition became steadily worse and the dyspnea a more prominent feature of the trouble. He was absent from work a good deal of the time, and he observed that the attacks always subsided when he stayed home and always recurred with his return to work.

No history was obtained of any similar trouble in the family, and the patient had not had any such illness before.

Physical Examination.—A man somewhat underweight presented typical chest signs of bronchial asthma. In all other respects he was normal.

Intradermal tests which included dust, fish glue, oysters, clam, flounder and mackerel were all negative.

It seemed obvious from the history that the attacks were due to some contact at the factory and inquiry brought out the fact that cuttlefish bone was frequently used as a mold for the molten gold in casting certain types of jewelry.

Extracts were made from the cuttlefish bone supplied by the patient. The bone was first pulverized, and 15 grams were added to buffered salt solution and allowed to stand for two days, filtered and found sterile. Half of the extract was boiled in an open flask for three minutes. These extracts were tested on the patient. The boiled extract gave a slight reaction with erythema; the unboiled extract gave a marked reaction. Control tests on sensitive and normal individuals gave no reaction.

Passive transfer of sensitiveness was easily demonstrated in the three cases tried, the boiled extract giving slight or negative reactions, the unboiled showing marked reactions.

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The patient was advised to change his plan of occupation and he obtained work with a firm which does not use this bone for molds. He has been free of all asthma except on two occasions when he purposely exposed himself to the dust and fumes of cuttlefish.

There are about one hundred varieties of cuttlefish, a species of squid belonging to the mollusk family. They are found in the warmer, coastal waters, and certain varieties are used for food in Italy, Greece, India, Japan and China. The bone forms the internal structure of the fish and varies with the species. That used commercially is imported from Tunesia.

A bulletin from the U. S. Department of Agriculture gives its commercial uses as follows:

1. By jewelers for engraving and molding of jewelry.
2. For filtering chemical products.
3. For dental powders.
4. Base for metal cleaning liquids and pastes.
5. Razor strop pastes.
6. In the manufacturing of powders used in conjunction with poultry foods.
7. By piano manufacturers.
8. For birds.

THE CONTINUOUS METHOD OF HAY FEVER TREATMENT*

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IN APRIL, 1927, Aaron Brown reported "A New Plan for Applying the Specific Treatment of Pollen Hay Fever,"[1] which he entitled "Perennial Treatment." In July of the same year, Vander Veer, Cooke, and Spain, in an article entitled "Diagnosis and Treatment of Seasonal Hay Fever,"[2] mentioned briefly the treatment by monthly injections. Since these original papers appeared, there has been, to my knowledge, very little further published regarding this method of treatment. I have no doubt that many men interested in hay fever treatment are using the year round method, or at least have knowledge of it. My object in this paper is solely to report my experiences in using this method and to encourage, if possible, its more extensive use.

By the continuous method of hay fever treatment is meant simply, the administration of the maximal, protective dose of pollen extract, at approximately monthly intervals throughout the year. This maximal, protective dose is of course reached by a series of doses of gradually increasing strength. It is usually the final dose attained in the first year's preseasonal treatment, although with this method, treatment may be commenced at any time of year.

The actual application of the method is as follows: The patient is treated preseasonally at intervals of three, five to seven days until his protective dose is reached just before the onset of the particular hay fever season. This dose is then repeated at intervals of seven to fourteen days during the season. Instead of discontinuing treatment at the close of the season, the protective dose is repeated in two weeks, then three weeks, and finally in four weeks. Thereafter it is repeated at monthly intervals until the next season, with certain modifications that will be mentioned shortly. In actual practice, it is not always possible to allow an interval of four weeks between injections of the protective dose in patients classed as *sensitive* and *very sensitive*, without risk of a constitutional reaction. Rather than shorten the interval, however, the dose is decreased somewhat in strength. The patient is then carried along at monthly intervals on this decreased dose until shortly before the next season, when it is stepped up to its protective strength by a few weekly injections. If, for example, in a patient quite sensitive to ragweed pollen extract, the protective dose reached is 0.3 c.c. of a 1-30 solution, the monthly maintenance dose is usually set at 0.3 c.c. to 0.5 c.c.

*Read before the Eighth Annual Meeting of the Association for the Study of Allergy, Detroit, June 23, 1930.

of a 1-100 solution. Then the following July, this maintenance dose is stepped up at weekly intervals until the maximal dose of 0.3 c.c. of 1-30 strength is again attained just before the onset of the ragweed season in August.

Many of the less sensitive patients, especially those that have had treatment continuously for many months, can tolerate the protective dose at monthly intervals without any such decrease in strength. The surprising ability of patients to tolerate large doses at such long intervals without reactions has been a constant source of wonder to me. This is due largely to the stability of our present-day pollen extracts, which retain their potency unchanged over many months. The extracts used are preserved with glycerol and kept constantly cold. When it is necessary to change from an old to a newly made stock solution, the proper dose of the next monthly injection is prepared by diluting the new extract with the old. For instance, one gives 2 parts new and 3 parts old extract the first month. The next month 3 parts new and 2 parts old, and the third month, the full dose of the new extract. In this way, the danger of a constitutional reaction from a new, more potent extract is minimized.

One feature of this method, of great convenience to patient and physician alike, is that doses of extracts of tree, grass, or weed pollens may be combined in the same syringe and given at one injection, thus obviating the necessity of multiple injections. After the tolerance dose of the various extracts is reached through proper preseasonal increases, the combined dose can usually be manipulated so that the total amount of fluid injected does not exceed 0.75 c.c. to 0.8 c.c.

Number of Cases and Classification.—This report covers a series of 65 cases, seen in private practice over a period of from two to four years. These cases were classified as to sensitiveness by means of skin tests with various strengths of the pollen to which the patient was clinically susceptible. On this basis, one was classed AA (extremely sensitive); 19 were A (very sensitive); 26 as B (average); 19 as C (less sensitive). Of these 65 cases, 34 were clinically sensitive to ragweed alone, while the remaining 31 were sensitive to grasses or to combinations of trees, grasses, and ragweeds. In 22 patients, seasonal pollen asthma was a definite symptom.

Duration of Treatment.—Of this group of cases, 7 were treated continuously over a period of four years, 27 for three years, and 31 for two years. No cases are included which have not been under continuous treatment for these different periods.

Constitutional Reactions.—There were 10 constitutional reactions in this series, resulting from the monthly interval plan of injections. The total number of monthly injections was roughly a little more than 2,000, giving a ratio of 1 reaction to about every 200 injections. These reac-

tions usually occurred because the patient forgot or neglected to come for treatment until an interval of some six weeks elapsed: in one instance, by mistake, a strong dose was given intradermally instead of subcutaneously. None of these reactions was severe or alarming; they all consisted of delayed urticaria, nasal symptoms, or mild chest tightness coming on several hours after the injection. They were all counteracted by ephedrin capsules with which each patient is provided in advance.

I wish to make it plainly understood that other constitutional reactions occurred in this series of cases, besides the ten mentioned—too many, in fact. However, these other reactions occurred during the course of the initial preseasonal treatment of these patients when we were pressed for time and attempted to crowd our dosage too rapidly. The almost complete absence of reactions during the winter months is in startling contrast to the unpleasant frequency with which they occurred during the periods of seasonal and preseasonal treatment.

In this connection, I must say that since the introduction of the practice of combining a small amount of adrenalin or a mixture of adrenalin and ephedrin with each dose of pollen extract, constitutional reactions have been very few in my experience. This method was first called to my attention last year by Balyeat,[3] and again amplified by Duke[4] in his excellent paper. This refinement of technic has done a great deal to remove our dread of the hated, unforeseen constitutional reaction.

Results.—In every instance, the result of treatment from the monthly interval injections has equalled and usually bettered the first year's preseasonal treatment. In no case has the patient discontinued treatment because he failed to get as much benefit the second or third year as he did the first. In fact, the clinical result improves, as a rule, directly in proportion to the length of continuous treatment; this is borne out by the increasing number of patients each year who elect to follow the continuous method.

Of this series of 65 cases, I consider that six have attained a clinical cure. None of them has had any symptoms for the past two seasons. However, their monthly treatment was kept up through last year for safety's sake. All of them originally gave strongly positive skin reactions: in four, the skin and conjunctival reactions are now negative, while in two, the conjunctival reaction is negative, although the skin test persists. These last two patients have had hay fever for twenty-five and thirty years, respectively. They no doubt had acquired much natural immunity. Four of the six have had continuous treatment for four years and two for three years. Of course, one cannot be certain that these six patients have attained a definite, permanent clinical cure until they have passed through one or two seasons without symptoms. My feeling is, however, that if symptoms do occur in the future, they will be so mild as to be negligible.

DISCUSSION

The advantages of the continuous method of treatment are as follows:

1. Treatment may be started at any time of the year, using mixed pollen extracts of trees, grasses, and weeds if necessary.

2. The number of office visits required is lessened appreciably.

3. Treatment is less likely to be interrupted by illness or summer vacations.

4. The results as compared with the interrupted method are invariably better after the monthly treatments have been sufficiently established.

5. There is good reason to believe that a clinical cure can be accomplished in much shorter time than by the interrupted or seasonal method. If one will assume the patient without previous treatment to have little or no immunity, one can picture his resistance or tolerance starting from a base line at zero. Step by step, it reaches a certain peak, through repeated preseasonal injections. Then, if the injections are discontinued after the season, one pictures the immunity gained as dropping back gradually toward the base line again. On the other hand, with the continuous method, the immunity is not allowed to recede but is kept at a high level indefinitely. In this connection, it should be remembered that the amount of pollen antigen the patient receives is much greater with the continuous method than with the interrupted method.

SUMMARY

1. Sixty-five patients have been observed under continuous treatment at monthly intervals from two to four years each. These patients showed the usual degrees of sensitiveness, varieties of clinical pollen sensitivity, and other allergic manifestations as would be found in any similar group of unselected hay fever cases.

2. Ten constitutional reactions occurred in slightly more than 2000 injections of pollen extract at monthly intervals—a ratio of one reaction to every 200 injections.

3. The result of treatment in each instance equalled or bettered the first year's preseasonal treatment.

4. Six patients have in all probability obtained a clinical cure: 4 after four years' continuous treatment and 2 after three years' continuous treatment.

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316 MICHIGAN ST.

A NASAL TEST WITH DRY POLLENS IN THE DIAGNOSIS OF SEASONAL HAY FEVER

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INTRODUCTION

THE diagnosis of seasonal hay fever is most often made by the use of the cutaneous or the intracutaneous method of testing. Experience has shown that both methods are subject to error and have been subjected to unfavorable criticism. Alexander,[1] particularly, has emphasized the common occurrence of localized allergy. He states, "certain organs only are receptive to allergens, and that unless the skin is so, no reactions can occur." "The skin will react in about 50 per cent of allergic patients." Numerous other observers have written of the deficiencies of the skin tests.

It is common experience to find cases of seasonal hay fever with absolutely negative skin reactions, and it is just as frequently an experience to find patients giving positive reactions to all or nearly all the allergens to which they are tested. Doubtful reactions are very frequent. Dermographic skins further complicate the picture. These experiences occur much more often in practice than are reported in the literature.

Because of the inadequacies of the skin tests, a number of workers have resorted to other tests. The hypodermic method is advocated by Kahn,[7] Bernton, and Balyeat.[2] The ophthalmic conjunctiva has been used also, but results have proved disappointing. Up to the present, the nasal test has been done by the use of extracts of pollens. Duke[5, 6] recommends this method in certain cases, especially where it is desired to determine the causative pollen of a series producing positive skin reactions. On the whole, results with this procedure have not come up to expectations. Duke[5, 6] states, "it is not difficult to conceive that the exposed tissue may react to dry untreated pollen even though it is insensitive to high dilutions." Isolated instances of the use of allergens placed or sprayed into the nose have been reported, but so far, to our knowledge, there has never appeared a report of any systematic use of the nasal mucosa as a criterion in the diagnosis of seasonal hay fever. This is most surprising, since the nose bears the brunt of the symptoms.

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This work received financial assistance from Mr. Simon Gelfand of Los Angeles, Calif.

We feel that in all cases of pollenosis, in which the nose is involved, the nasal mucosa is the final judge of the hypersensitivity, and that dry pollens used as allergens in the nose closely approximate conditions as they occur in nature.

THE TEST

The following materials and instruments are required for the test: Dried pollens, ephedrine 3 per cent and 1 per cent solutions, De Vilbiss powder blowers (No. 36), normal saline, nasal sprayers. Each species of pollen is placed in a separate powder blower, not less than one gram being put in any one blower. The tests are performed at a time other than the patients' hay fever season, when the pollens to which they are suspected of being sensitive are not in the air. At each visit one or two sprays of pollen are blown into one nostril. Patients are kept in the office for half an hour after the test is performed.

When pollen is sprayed into the nose, the immediate effect in all cases, whether sensitive or not, is some suffusion of the eyes, particularly of the eye on the same side as the nostril used, slight burning, perhaps a tingling sensation in the nose, tingling pain at the vertex or occiput, which is never severe, slight mucus formation in the nose, and perhaps one or two sneezes. If the patient is not sensitive to the particular pollen sprayed, these symptoms subside in a few minutes and no further symptoms occur. Where hypersensitivity is present, hay fever symptoms of varying severity follow. Those that are very sensitive react very shortly after the test is performed. Most cases react within a few minutes. However, symptoms have appeared as late as fourteen hours after the test; so that sittings should not be more often than every other day. Usually, the more rapid the onset of symptoms, the greater their severity and duration, but this is not invariably so. As a rule, symptoms, except in the most severe reactions, are limited to the side on which the pollen was sprayed. As soon as definite symptoms appear, the nose is washed with saline until all the pollen is washed out, after which it is sprayed with ephedrine solutions. These procedures usually abort the attack or modify its severity to a large extent. In a small number of instances we have observed the attack to persist over a long period; in one case for two weeks; in another for ten days. In each instance, however, there was a daily diminution in severity. Of course, no subsequent testing is done until all symptoms from the previous one have entirely disappeared.

REPORT

More than forty-five hay fever patients have been tested by this method. Trees, grasses, ragweeds, and other pollens have been used. The twenty patients on whom the tests with all fall pollens were completed were selected for this report. We wish to state that we have

TABLE I

COMPARISON OF NASAL AND SKIN TESTS*

PATIENT NO.	NASAL TESTS				SKIN TESTS			
	COCKLEBUR	MARSH ELDER	COMMON RAGWEED	GIANT RAGWEED	COCKLEBUR	MARSH ELDER	COMMON RAGWEED	GIANT RAGWEED
1	Neg.	Neg.	Pos.*	Pos.	II	III	IV	IV†
2	Very mild	Neg.	Pos.	Pos.	I	I	IV	IV
3	Neg.	Neg.	Pos.	Pos.	I	I	IV	IV
4	Pos.	Neg.	Pos.	Pos.	xx	xxxx	xxxx	xxxx
5	Neg.	Neg.	Pos.	Pos.	xx	xxxx	xxxx	xxxx
6	Very mild	Neg.	Pos.	Pos.	–	xxxx	xxxx	xxxx
7	Neg.	Neg.	Pos.	Pos.	–	xxxx	xxxx	xxxx
8	Neg.	Neg.	Neg.	Pos.	I	I	II	II
					x	xx	xxx	xxx
9	Pos.	Neg.	Pos.	Pos.	0	0	0	0
					–	–	–	–
10	Neg.	Neg.	Pos.	Pos.	I	III	III	III
					xx	xxx	xxxx	xxxx
11	Neg.	Neg.	Pos.	Pos.	0	0	0	0
					–	–	–	–
12	Neg.	Neg.	Pos.	Pos.	0	0	I	II
					xx	xx	xx	x
13	Neg.	Neg.	Very mild	Very mild	xxx	xxxx	xxx	xxx
14	Pos.	Neg.	Neg.	Neg.	II	0	II	III
					0	x	x	x
15	Neg.	Neg.	Pos.	Pos.	xxxx	xxx	xxxx	xxxx
16	Mild	Mild	Pos.	Pos.	0	0	0	0
					–	–	–	–
17	Pos.	Neg.	Pos.	Pos.	0	0	0	0
					–	–	–	–
18	Neg.	Neg.	Pos.	Pos.	xx	xxx	x	x
19	Neg.	Neg.	Neg.	Neg.	II	I	II	II
					–	x	x	xx
20	Neg.	Neg.	Neg.	Neg.	II	II	0	0
					–	–	x–	x
Control	Neg.	Neg.	Neg.	Neg.				
Control	Neg.	Neg.	Neg.	Neg.				

*Positive is denoted by very definite symptoms of hay fever, as itching in nose, eyes, throat, suffusion of eyes, sneezing, running nose, excess mucus, stoppage of nose; of very definite degree.

†Roman numerals and 0 indicate scratch test; x and – indicate intradermal test. Values = intensity of reaction. Controls were used with each type of test. No test was considered xxxx unless wheals with pseudopods were present. No test was considered positive unless definitely larger than the control.

obtained invaluable information on spring and summer cases as well. These observations will be published later.

DISCUSSION

From this study (Table I) it is quite evident that cutaneous reactivity accompanying clinical hypersensitiveness bears neither a constant nor a quantitative relationship to the clinical picture. It may be absent in the presence of allergic disease or present when there are no clinical manifestations of hypersensitiveness. Marsh elder pollen illustrates this statement. (Tables I and II.) Of the twenty hay fever cases, one mildly positive reaction was obtained with the nasal method, whereas in eighteen of these cases, a positive response was obtained in the same individuals with similar amounts of the other pollens. On the other hand, only six negative skin reactions were obtained with this pollen. In fact, in many cases the dermatologic response was as large and in some cases larger than that of the dominant nasal reactors. The cutaneous cocklebur reaction was usually smaller than that of the marsh elder. There was a total absence of skin sensitivity in four (20 per cent) of clinically known and nasal-tested positive allergic cases. In the light of past experience, uniformity of results with the two methods of skin testing was not expected, and neither method proved more valuable than the other. Note cases 8, 9, 10, 11, 12, 14, 16, 17, 19, and 20.

TABLE II

SUMMARY OF RESULTS OF NASAL TEST

POLLEN	NUMBER CASES TESTED	NUMBER POSITIVE REACTIONS
Cocklebur	20	7
Marsh Elder	20	1
Common Ragweed	20	16
Giant Ragweed	20	17

The ragweeds alone give positive reactions in eleven of the twenty cases. In only one case (No. 8) was a reaction obtained to one ragweed and not to the other. In six cases, reactions to cocklebur were obtained in addition to the ragweed reactions. The cocklebur reaction was greater in intensity than that of the ragweeds in one case (No. 14). In fact, in three of the six positive cocklebur responses, the symptoms were very mild and were listed as such. In only one case was marsh elder indicted as a cause of fall hay fever.

Certain of these cases require special consideration. Case No. 14 (mentioned above) reacted to cocklebur only. The cutaneous responses in this case were not very informative. This is the only instance in which a reaction was obtained to a pollen other than the ragweeds. We have been unable so far to explain cases Nos. 19 and 20. Both patients

are victims of seasonal hay fever, starting in early spring and continuing to the frost. Both were tested by the nasal method with fifteen other pollens growing in this locality. Negative reactions occurred in each instance. Skin tests with foods, house dust, and epidermals were also negative.

CONCLUSIONS

1. A nasal test with dry pollens is described. Twenty fall hay fever cases were studied with this test.

2. Cutaneous reactivity accompanying clinical hypersensitiveness was found to bear neither a constant nor a quantitative relationship to the clinical picture.

3. Positive nasal reactions were obtained in eighteen (90 per cent) cases.

4. The ragweeds were found to be the dominant reactors. In sixteen of the seventeen positive ragweed cases, the response to both species was almost identical. One patient reacted to giant and not to common ragweed.

5. Cocklebur was found to be a minor and complicating factor in fall hay fever.

6. Marsh elder rarely produces symptoms.

7. The nasal test with dry pollens is the most physiologic method yet devised for the diagnosis of seasonal hay fever.

8. Despite its greater discomfort to the patient and the increased amount of work to the physician, the nasal test is practical. It is much more specific and very much more convincing both to patients and physicians than any of the other test methods.

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A CRITICAL ANALYSIS OF THE INFORMATION OBTAINED FROM HAY-FEVER SUFFERERS*†

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PRELIMINARY REPORT

WHEN we analyze the steps in the advance in knowledge of almost any medical disorder, we are amazed to find that we have been so slow to pick out important, plainly evident leads and have taken the longest way around to reach our goal. We often find that the patients, although untrained in clinical observation, give important suggestions which should have been considered. In this paper I am submitting data taken at random from the initial histories of over 300 typical hay-fever sufferers. Some of this data may be irrevelant but I hope that, taken as a whole, it will stimulate more critical thinking about our sufferers from pollen disease.

RACES AND NATIONALITIES

The individuals of any race or nationality may have pollen disease, and the number of each seen by any one person depends on the locality in which the observations are made. Chicago with its cosmopolitan population yields this type of patient from almost all races and nationalities.

OCCUPATION

As so many of those who have pollen disease are children or young adults, the significance of occupation in this analysis may be considered questionable.

AGE

The age of the onset of pollen disease in many patients is difficult to determine, as the correct diagnosis may not have been made during the first few years of trouble. The failure to make a diagnosis may have been due to the mildness of the symptoms or to unfamiliarity with the symptoms. Then too, many patients do not consult a physician until some complication, as asthma, comes on years after the onset of their first symptom. As so much is now being said in newsprint and over the radio about the symptoms of pollen disease, most new patients

*This work was aided by a grant from the Committee on Scientific Research of the American Medical Association.

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Read before the Eighth Annual Meeting of the Association for the Study of Allergy, Detroit, June 23, 1930.

have a tentative diagnosis made early in the disease. Either this familiarity with symptoms is resulting in more diagnoses being made, or pollen disease is decidedly on the increase.

In the group of patients reported here the onset of symptoms of decades is as follows:

1st	23 per cent
2nd	35 per cent
3rd	26 per cent
4th	12 per cent
above 4th	4 per cent

This shows that 58 per cent of all cases seen are in the first two decades.

I have considered also the question of prenatal and early postnatal influence. The birthdays of this group being reported are spread about equally throughout the year. It would seem then that one who is born just before, during, or just after a pollinating season is no more likely to have pollen disease than those born several months later. Many of those who are sufferers may have had no pollen exposures until late in life.

ASTHMA

Fifty-four per cent of this group of patients have had definite asthmatic attacks, and another 7 per cent have had questionable attacks. Eighty-three per cent of those having asthma have it only during the pollinating season, and 17 per cent have it at any time of the year. Of this last group more than one-half have other known sensitizations, such as that due to food, animals, etc. Twenty-two per cent of this asthmatic group had asthma the first year that pollen symptoms were present; 12 per cent had asthma before having pollen symptoms, and 7 per cent have never had any other pollen symptoms except seasonal asthma.

TYPES OF POLLEN DISEASE

In the Chicago area there are three main groups of pollens which produce symptoms, namely, trees, grasses and weeds, and these groups are rather sharply limited as to season. The trees pollinate in March and April, the grasses in late May, June and most of July, and the weeds from the middle of August to the first frost, about October 1. This limitation of the pollinating season of these groups allows the grouping of patients as follows:

7 per cent have grass pollen symptoms only.
65 per cent have weed pollen symptoms only.
28 per cent have combined grass and weed pollen symptoms.
3 per cent of these also have tree pollen symptoms.

Grouping in another way, we have the following figures:

80 per cent of those with grass pollen symptoms also have weed pollen symptoms.

30 per cent of those with weed pollen symptoms have grass pollen symptoms.

Only 4 per cent of this 80 per cent with grass pollen symptoms give histories of having had the weed pollen symptoms prior to the grass pollen symptoms.

In 76 per cent of this 80 per cent the weed pollen symptoms followed the onset of the grass pollen symptoms.

Why do we have this great difference in these two groups? Is it not probable that mucous membranes of the respiratory tract have not recovered from the injury caused by grass pollens in July before the weed pollens strike them in August, three weeks later?

Those who start with the weed pollen symptoms have about eight months to recover from the injury from weed pollens before exposed to grass pollen.

ILLNESSES AND OPERATIONS

The illnesses and operations of such a group obviously vary greatly because of the variation in age, and these are considered here only for the purpose of establishing the possible relationship between them and the onset of pollen disease.

Ninety-one per cent of this group above ten years of age has had 3 or 4 of the childhood diseases, namely, chickenpox, measles, mumps, and whooping cough.

Seventy-three per cent of this group below ten years has had these diseases.

In addition to the childhood diseases, 9 per cent of this group has had scarlet fever; 6 per cent of this group has had diphtheria; 2 per cent of this group has had typhoid; 20 per cent of this group has had influenza; 15 per cent of this group has had eczema; 11 per cent of this group has had urticaria.

Only 7 per cent of all of these illnesses occurred just before or during the pollinating season when the patient had the first pollen symptoms.

The only operations considered are those about the nose and throat.

Seventy-five per cent of this group has had tonsils removed; 58 per cent of this group has had adenoids removed; 18 per cent of this group has had some nasal surgery.

Eighty-eight per cent of the tonsil and adenoid surgery was done before the onset of pollen disease, and 84 per cent of the nasal surgery was done after the onset of pollen disease.

Only 10 per cent of those who had nose or throat surgery done before the onset of symptoms had their operation just before or during that pollinating season when the patient had the first pollen symptoms.

OTHER SENSITIZATIONS

While giving a pollen disease history 10 per cent of the patients will state that during their pollen season they are not able to eat certain foods or inhale certain kinds of dust without initiating or increasing noticeably their symptoms. I have skin-tested many of these patients and have found positive reactions with many of the suspected foods and dusts, both during and outside their pollen season. There may be no history of symptoms from such food or dust outside of their pollen season, but the added pollen irritation precipitates severe symptoms. In patients with such histories and in those where adequate treatment has not given the expected relief, food and dust tests should always be done. It may be the best plan to make complete tests routinely.

The most commonly implicated foods are peaches, pears and melons, and the most common dusts are horse, cat and dog hair, orris root, and feathers. However, any other food or dust may be found to give reactions.

HEREDITY

The relationship of heredity in pollen disease has been discussed by many writers, and most of them have found that about 50 per cent of their patients have relatives with some allergic manifestation. Most of the statistics dealing with this subject are not detailed enough or are not adequately explained. They are usually based on one question, namely, does any member of your family have hay fever, asthma, eczema or urticaria? There is no indication that the place of residence, the chances for exposure to pollens or other factors have been considered. From the statistics that are published we cannot tell how many of the relatives of those with no family history of allergy have had no exposure nor can we tell how many of the relatives of those with definite family histories of allergy have had excessive exposures. I believe that these angles should be investigated thoroughly before statements as to heredity are made. I have seen quite a number of Chinese, Japanese, and Italian patients with pollen disease. None of their relatives live in this country and I am rarely able to get any history of allergy. On the other hand I often find patients, many of whose relatives have some manifestation of allergy, and I almost invariably find that this group lives under conditions where massive exposure is common and unavoidable. There are several factors other than heredity which should be considered. I have already spoken of the relationship of some preceding illness or operation to the initial attack of pollen disease. In addition, I find quite an appreciable percentage of patients, 12 per cent, whose initial attack

followed some unusual massive exposure. For example, one patient, a carpenter, had his first definite attack while building on a lot covered by ragweed, several had the first definite symptom during a long automobile or train trip on a windy, dusty day; several children had their first definite symptom while on a hiking or camping trip, several had their first definite symptom after moving from one section relatively free from pollen to one with a heavy atmospheric pollen count, and so on. The histories of initial symptoms at a time of massive exposure under unusual circumstances in so many patients raise these questions. Are we all potentially allergic and waiting for some massive exposure to start off our typical symptoms? Do some of us possess constitutions which are less resistant to massive exposure?

TREATMENT

Thirty-two per cent of those above twenty years of age have had some form of so-called specific treatment. The type of treatment varied greatly, specific and nonspecific; preseasonal, seasonal and continuous—single pollen extracts—to shotgun mixtures; from two to fifty injections annually; subcutaneous, intracutaneous, and intramuscular injections; five injections daily to one injection a month—and so on. In addition there are the various symptomatic remedies used.

11 per cent of those so treated had had severe constitutional reactions.
7 per cent had had severe local reactions with the first injection.
15 per cent had had no local reaction of any kind.
7 per cent felt that they had been harmed by treatment.

The results of these treatments as reported by the patient were, of course, generally poor. We may ask ourselves the questions: Where does the fault lie? How are we to remedy this situation?

I have two suggestions to make: first, that no patient should be treated until he has given a complete history and has had adequate tests; second, that those who are supervising the treatment should familiarize themselves with this particular type of treatment. The careless use of pollen extracts is almost as harmful as the careless use of insulin in diabetes.

There are many other important points that have been considered, but lack of time will not permit me to discuss them here. Some of these are the effect of pregnancy, puberty, menopause, spontaneous disappearance, other complications than asthma, basal metabolism, blood pressure, blood chemistry, and so on.

SUMMARY

This review of the information given by those with pollen disease may be summarized as follows:

1. Any race or nationality may have pollen disease.

2. Definite symptoms of pollen disease may appear at any age. Fifty-eight per cent of those studied here were below twenty years of age.

3. Seventy-two per cent of those studied have only one type of pollen disease; 7 per cent have grass pollen symptoms only; 65 per cent have weed pollen symptoms only; and 28 per cent have both grass and weed pollen symptoms.

4. Seven per cent of those studied suffered from some acute illness just before the first symptom of pollen disease appeared.

5. Ten per cent of those studied had some surgical operation about the nose or throat just before the first symptom of pollen disease appeared.

6. Typical bronchial asthma occurred in 54 per cent of those studied.

7. Food sensitizations are found in many of pollen disease sufferers.

8. Thirty per cent of those studied have relatives with symptoms of allergy.

9. Massive exposure to pollens may be an important factor in precipitating pollen disease.

In closing I wish to make a plea for the more careful study of those who suffer from pollen disease.

RELIEF OF BRONCHIAL ASTHMA FOLLOWING LOBAR PNEUMONIA

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THE solution of the mechanism of allergy is still clouded by a multitude of conflicting observations. As in the study of other problems, many theories and hypotheses have been advanced to serve as a means to an end, and one of these concerns atopy, a clinical subdivision of allergy. Coca[1] has coined this term to "designate the inherited hypersensitiveness of human beings, which sensitiveness, though inherited most probably as a Mendelian dominant character, manifests itself in a number of clinical forms, the recognized ones being hay fever (atopic rhinitis), bronchial asthma, urticaria, eczema, angioneurotic edema, and gastrointestinal disturbances." It is quite evident that the definition, involving as it does the factor of inheritance, excludes the use of animals for experimental purposes, since up to the present time no form of inherited allergy has been recognized in them. In other words, all forms of hypersensitiveness to proteins in animals have been induced. For this reason much of the data in the study of atopy will have to be obtained by observations in humans.

Although asthma and hay fever are recognized as definite allergic disturbances, their classification under atopy as a distinct and separate entity lacks universal agreement. Indeed, the pathology and physiology of atopy are somewhat more obscure than those of allergy, and one of the questions presenting a wide difference of opinion is the relation of infection to asthma. It has been shown that bacterial proteins are capable of causing allergy after active and passive sensitization and, more applicable to this paper, that pneumococcal protein can act in the same capacity. That bacterial proteins possess antigenic properties in the production of allergic reactions experimentally is universally accepted, but a similar rôle in the production of atopy is not established, even though atopy is a form of allergy. Karsner[2] states that "there appears to be no clear experimental evidence as yet to support the conception, in the true sense, of a hypersensitiveness to infection. Nevertheless, there are phenomena in infectious disease that strongly suggest this possibility." An observation on the influence of infection in two patients with asthma forms the basis of this paper.

In order to diagnose bronchial asthma, Cooke[3] insists that its atopic nature be proved by the fulfillment of several postulates, among which is the production of a positive skin reaction with a substance which bears a definite relationship to the production of symptoms. This latter

postulate is readily satisfied in those cases caused by extrinsic substances, such as pollens, food proteins, animal emanations, house dust, etc., and the specific relationship between the isolated proteins and symptoms is so evident and definite that it is universally acknowledged and needs no further verification. But when bacterial proteins are utilized in testing patients classified on clinical grounds as "bacterial" in type, the results are so indefinite that the existence of such a group is questioned.

Perhaps it would be in order to consider briefly the relationship of respiratory infections to asthma and the reasons for making a subdivision of bacterial asthma clinically. Chronic bronchitis occurs very often in association with asthma, the relationship of the two varying, in one case the bronchial infection being superimposed on a chronic, allergic, asthmatic condition; in the other, preceding and accompanying each attack of asthma in which no allergic factor is demonstrable with any of the test proteins. For instance, patients who are sensitive to ragweed pollen and suffer each autumn with asthma often develop eventually a bronchitis which remains long after the first frost has brought an end to the production of pollen, and which tortures the patients with continued asthmatic symptoms. Another group, subject to frequently recurring "colds," exhibits asthmatic symptoms with each infection, the severity of the two being roughly proportional. In the former case, the bronchitis is a complicating infection in a person who is allergic to an extrinsic protein, and the infection for some reason maintains typical asthmatic symptoms. In the latter case, the bronchial infection appears to be the primary affection, and the asthmatic symptoms to be dependent upon its presence. With these considerations in mind, one can readily understand the reason for classifying patients with asthma in the Asthma Clinic of Bellevue Hospital as follows[4]:

1. Bronchial asthma; simple, uncomplicated.

2. Chronic bronchial infection with its complications, simulating bronchial asthma.

3. Bronchial asthma, complicated by chronic bronchitis.

4. Chronic bronchitis complicated by bronchial asthma, and not merely simulating it, including those who have acquired sensitization to bacterial proteins. This last group, it must be mentioned, is considered only "possible" by the authors, who, with the majority of authorities, feel that incontrovertible proof for the existence of atopy due to bacterial proteins is still lacking. The patients in this group have typical asthmatic symptoms with the cardinal one of prolonged expiration only when bronchial infection is present; therefore, they do not belong to group 1; the cardinal symptom excludes them from group 2, in which sibilant and sonorous râles are present but not the typical prolonged expiration; and they are excluded from group 3 by the fact

that the attacks bear no relation to pollen, food proteins, house dust, animal emanations, etc., and occur whenever and wherever the patient is afflicted with a "cold" or bronchitis. Whether in these cases the infection acts merely as an aggravating cause of symptoms in patients with asthma due to some other protein, just as exposure to cold or dust cause sneezing bouts during the hay fever season, or whether the bacterial protein in itself is the cause of the allergic reaction, is the problem to be solved. As Rackemann[5] expresses it: "There is a group of patients who have attacks of asthma quite regularly every spring and fall, each attack lasting for a few days or a week. The fact that these attacks are not preceded by change in environment, diet or occupation makes it unreasonable to assume that any foreign protein is responsible and renders the diagnosis of 'bacterial asthma' logical."

Bearing on this question is a clinical observation which I noted in two patients, who, having had severe and long-standing asthma, clinically of the bacterial type, showed an almost immediate and absolute cessation of symptoms following lobar pneumonia.

CASE 1.—M. R., male, first seen April, 1927, age forty-one years, born in Scotland, gives a history of asthma since childhood, the symptoms then being severe enough to necessitate absence from school for weeks at a time. His father had asthma, also a child of his father's brother and a child of his sister.* At the age of seventeen years he went to Africa and enjoyed complete freedom from symptoms during his residence in that warm and dry climate. On his return to Scotland the asthma returned at once. In 1911 he came to the United States and had suffered badly since then continually. In April, 1927, he had a severe attack of lobar pneumonia, being delirious and cyanotic from the fourth to the eleventh days, after which the temperature dropped by rapid lysis. A smear of the sputum showed the presence of pneumococci, but typing was not done nor was serum given. Since then the patient has been free of asthmatic symptoms except for an occasional "cold" attended with slight wheezing and râles, but no dyspnea. Up to the present time he has been working in complete comfort, which he had been unable to do previously.

CASE 2.—M. K., female, age sixty-three years, first seen November, 1925. She had severe asthma for the preceding fifteen years following a "cold." No history of allergy in the family, which is in keeping with the late onset. In 1924 she had slight relief temporarily while receiving injections of stock catarrhal vaccine. In 1925 she came under my care and claimed to have had still greater relief following injections of autogenous vaccine containing streptococci, staphylococci, pneumo-

*It has been shown that the age of onset of allergic symptoms is determined by heredity [6], the more firmly established allergy being in one's ancestors, the earlier the onset, and this case is illustrative.

cocci and M. catarrhalis cultured from her sputum, the benefit lasting about two months after the last injection. In February, 1926, she had severe lobar pneumonia attended with Cheyne-Stokes respiration and coma, ending on the thirteenth day in typical crisis. For the next four months the symptoms of asthma were entirely absent but returned gradually and at intervals, until they were again severe and constant in the latter part of 1927. During January, 1928, a second attack of lobar pneumonia threatened the patient's life, and ended by lysis. In both instances the sputum was filled with pneumococci which were not typed. Treatment was symptomatic, no serum having been given. Since then the patient has lived comfortably and has had no symptoms except slight wheezing with each "cold." During the past year the lungs have become the seat of tuberculous infiltration.

Here, then, are two asthmatic patients whose continuous attacks of twenty-eight and fifteen years' duration respectively come to a sudden and striking end following lobar pneumonia, the causal relationship of the two being unquestionable. Inasmuch as the only foreign protein involved in the cause of illness of both patients was that supplied by pneumococci, and since the only means of influencing asthma to any extent, aside from the use of palliative drugs, is through the action of proteins, we are led to assume that the beneficial results in these cases were due to the presence of bacterial protein, and for the sake of argument, that the reaction was specific (pneumococcal protein). For if it were nonspecific, then any infectious febrile condition, such as typhoid fever, puerperal sepsis, malaria, etc., should produce the same result, but such cases, as far as I could find, have never been reported. To prove the establishment of a specific immunologic reaction by technical procedures in cases of atopy still awaits solution of the manner in which immunity is established; the tests to date give varying results in different hands and are inconclusive. For instance, Walker[7] could find no correlation between the cutaneous reaction, the agglutinin or precipitin tests, and the recovery of the organisms from the sputum of patients suffering with the bacterial type of asthma who showed satisfactory results with vaccine therapy. Dealing with a more clear-cut group of asthmatic patients sensitive to ragweed pollen, in whom specific hyposensitization with pollen extracts caused relief in symptoms, Cooke[8] was unable to show any change in cutaneous reaction at the end of treatment. Levine and Coca[9] found that the allergic reagin, instead of being decreased after successful immunization, as would be expected, was actually increased. Evidently, the only conclusion to be drawn from these findings is that the establishment of increased tolerance in atopy by specific treatment rests on a mechanism differing from desensitization in other forms of hypersensitiveness. In the present stage of knowledge, it is doubtful if any useful information could have resulted had all the common tests used in allergic studies been performed in the cases re-

ported here; naturally, neither anticipating the pneumonia nor the beneficial influence on the asthma, they were not even considered.

To prove that pneumococcus protein can produce an atopic reaction, a definite relationship between pneumococcus invasion and the onset of asthma must be demonstrated. There are many cases reported in which pneumonia has immediately preceded the initial symptoms of asthmatic bronchitis; also other respiratory infections which may have been due to the pneumococcus.[10] It might be argued that pneumococci are present in everyone at all times, and that this fact would be difficult to correlate with the presence of pneumococcal atopy in some persons and not in others, and with the presence of symptoms at some times and not at others in those so affected. Referring to Case 1 as an example, one notes that the patient's symptoms were present in Scotland and in the United States but not in Africa. Analagous to this is the occurrence of considerable sneezing only during the pollinating season in patients with hay fever when exposed to much dust or to instrumentation of the nasal mucosa; during the rest of the year the same stimuli cause normal responses. In other words, a nonspecific stimulus is capable of causing marked symptoms when the shock organ is in an atopic state. Applying this to Case 1 and assuming that the shock organ (bronchial system) was in a constant state of atopy, one notes that symptoms were present in the raw and changeable air of Scotland and the eastern seaboard of the United States, but not in the warm and equable climate of Africa. Climatic variations, therefore, act as nonspecific stimuli. But when we attempt to reason why some persons become atopic and others do not, our only answer is one begging the question, i.e., only those persons become allergic who show, in the words of one author, a "peculiar tendency toward abnormal bioplastic activity of the body cells," i.e., inherit the abnormal ability of certain cells (shock tissue) to become allergic, and the reaction appears in the presence of the atopen through the intervention of some inciting cause.

The results following the use of vaccines also support the theory of the production of a specific type of immunity. Although some men have had unsatisfactory results, and therefore do not believe that bacterial proteins are true etiologic factors in the production of hypersensitiveness, a greater number report marked relief following the use of vaccines which caused a definite skin reaction, the extent of relief varying roughly in proportion with the intensity of reaction, and conclude thereby that hyposensitization rests on a specific immunologic basis.

This line of reasoning might be criticized by referring to the cures reported by the use of nonspecific vaccines, and by chemicals such as tuberculin and sulphur. Von Jaurreg and others noted many years ago that intense fevers caused considerable relief in a number of patients with general paresis, and the malarial treatment of pareties which once rested on empiric grounds is now recognized as a scientific procedure, the

mechanism of which is explained by the cellular reactions in the brain. But as previously noted, relief of asthmatic symptoms following fevers has, to my knowledge, not been reported in the literature, and the fact that the patients reported in this paper had high fever during the course of pneumonia appears to be of much less significance than the presence of a pneumococcal infection. Considering, nevertheless, the reports of favorable results produced with nonspecific vaccines and chemicals, it soon becomes evident to one reading over a number of papers that the beneficial effects occur either in a very small percentage of cases, or are quite temporary, or are present only through the enthusiasm of the observer. This is in contrast to the frequent and more marked relief, for a varying length of time, obtained by the majority of workers by the use of specific vaccines giving skin reactions. The evidence at hand seems to support the probability that a specific reaction is involved in the treatment of asthma with bacterial proteins, and the beneficial effect of lobar pneumonia in the cases reported here certainly strengthens this belief. Perhaps the happy course of events following the overwhelming infection is an indication that a change in the vaccine dosage might lead to more successful results in those patients who are unfortunate enough to suffer from the bacterial type of asthma.

SUMMARY

The marked relief in symptoms of two patients suffering with severe bronchitis and bronchial asthma over a period of thirty-eight and fifteen years respectively, immediately after recovery from lobar pneumonia, supports the theory that bacterial proteins bear an intimate relationship to the so-called bacterial type of asthma, recognized as such clinically, and that treatment of such cases with autogenous vaccine therefore rests on a rational basis.

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CASE REPORT ILLUSTRATING THE NONSPECIFIC INDUCTION OF LOCAL AND GENERAL REACTIONS IN A HAY FEVER (SYPHILITIC) PATIENT BY THE INTRAVENOUS INJECTION OF NEOSOL

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AS IS well known the intravenous injection of any of the organic arsenical preparations used in the treatment of syphilis is not infrequently followed by anaphylactic- (or allergic-) like reactions. It is, I believe, the usual practice to find that these may be controlled by the use of adrenalin.

The following case report illustrates this phenomenon in an unusual manner and suggests that possibly it is more likely to take place in those syphilitic patients whose history gives evidence of some type of clinical allergy, such as hay fever, asthma, eczema, etc.

The patient, a female, thirty six years of age, was under preventive treatment for hay fever by periodical injections of pollen solutions, the injections being given subcutaneously in the upper arms. On account of a certain amount of indefinite ill health and a "nerve deafness" a diagnosis of syphilis was made which was confirmed by a "strongly positive" Wassermann reaction.

Shortly after the intravenous administration of Neosol was begun, flushing with beads of perspiration and swelling of the face were noticed. At the same time wheals were seen to form at various areas over both upper arms. The patient complained of a ringing in the ears with a sense of fullness in the head. The injection was discontinued, and it was found that approximately 0.25 gm. had been given. The individual wheals spread quickly and coalesced with excessive swelling and a reddening of the arms. The few general symptoms subsided fairly rapidly, although the arms remained tense and excessively swollen for many hours and had not completely subsided in three days.

The second intravenous injection of Neosol was given eleven days after the first. In two minutes after the insertion of the needle in the vein multiple wheals began to form over both upper arms, and rapidly enlarged and coalesced. With their appearance, adrenalin was injected subcutaneously, and the administration of Neosol was continued until 0.36 gm. had been given. The intensity of the wheal formation and the associated local swelling were much less than on the former

occasion, but head symptoms were more marked; in addition, a feeling of numbness of the legs appeared and persisted for some time.

The pollen solutions had been injected only in a relatively small space above the elbows, and this was the only area in which the wheals appeared. It would thus seem likely that some fraction of the pollen had been "anchored" by the sensitized epidermal cells each time the pollen injections were made. While the systemic symptoms were no doubt due to the same underlying phenomenon of increased permeability of the vessel walls, the arms showed this much more intensely than any other part of the body. Both the systemic and local reactions were simultaneously induced by the introduction into the circulation of Neosol, a substance by itself nonspecific to the pollen sensitive cells.

No further administration of any of the arsenical preparations was attempted, although finally several negative Wassermann tests were obtained after the use of bismuth.

The value of pollen desensitization has been sufficient to have the patient continue with this. With any tendency to a reaction a sense of distress in the ears appears.

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Department of Reviews and Abstracts

Selected Abstracts

Bullowa, J. G. M., and Jacobi, M.: Fatal Human Anaphylactic Shock. Arch. Int. Med., **46**: 306, 1930.

A detailed report is given of a case of fatal anaphylactic shock following a single injection of diphtheria antitoxin. Autopsy was performed seven hours postmortem. The autopsy report, the microscopic examination, and the bacteriologic examination are given at considerable length. The chief findings consist of acute pulmonary emphysema, dilatation of the right side of the heart, general venous stasis and visceral congestion; the left side of the heart was contracted and empty. The principal microscopic changes were noted as a thickening of the arteriolar wall, especially in the lungs.

A review of the literature of thirteen other reported autopsied cases of fatal anaphylactic shock is given in some detail. These cases, like the one reported by the authors, presented clinical manifestations comparable to anaphylactic shock in experimental animals. The postmortem observations, however, showed no marked constancy. Emphysema, in differing degrees of severity, was noted in six cases, dilatation of the right side of the heart was noted in one case (besides the one reported by the authors). The liver was congested in four instances, the spleen in three cases, the kidney in three, the brain in one, the gastrointestinal tract and peritoneum in one and the adrenals in one. There did not appear to be any correlation between the presence of previous anaphylactic symptoms or injection of foreign protein, with the presence of thymic or hyperplastic lymphoid tissue. The anatomic observations varied considerably, but emphysema and general venous stasis and parenchymal congestion were prominent. Commenting upon their own case report, the authors state:

"The extreme dilatation of the right side of the heart with general congestion and markedly contracted left side of the heart devoid of fluid contents or blood clots seem further to substantiate the belief that the cause of death as anaphylactic shock is failure of the right side of the heart and inability to maintain pressure in the pulmonary system as the result of obstruction of the arteriolar blood bed, as indicated by the experimental work cited."

Balyeat, R. M., and Brittain, F. L.: Allergic Migraine. Am. J. M. Sc., **180**: 212, 1930.

The study is based on fifty-five cases of migraine, the ages of the patients ranging from six to sixty-eight years. In 85.4 per cent of the cases, allergy was found to be a hereditary factor. The hereditary factor is not necessarily migraine itself, but might be asthma, hay fever, gastrointestinal disturbance, etc., or any one of the allergic manifestations referable to a specific sensitivity to one or more foreign proteins.

Many conditions may play a part as predisposing factors in migraine, such for instance, as physical fatigue, mental fatigue, disturbance of the special senses, etc., but the exciting factor seems to be a specific sensitivity to one or more foreign proteins. The severity and frequency of the attacks vary greatly with the individual. Five case reports are given in which the patients were relieved of their attacks by the elimination of the offending proteins, which, in these instances, were foods of the common variety. Patients were tested by the scratch method for sensitivity to proteins and checked by the intradermal method. Results of the treatment in the series of fifty-five cases showed 52.7 per cent obtained from 85 to 100 per cent freedom from symptoms, and 18.2 per cent received more than 60 per cent relief.

Winans, H. M.: Reaction to Pantopon (Pantopium Hydrochloricum) Simulating Protein Sensitization. J. A. M. A., **95**: 199, 1930.

A report is given of a patient who gave both a local and a severe constitutional reaction to pantopon. The patient had suffered from dysentery, and to secure rest a hypodermic was given. The patient had stated that morphine disagreed with her. One-sixth grain (11 mg.) of pantopon was administered hypodermically. Within a few minutes a wheal appeared at the site of injection and increased rapidly in size. Erythema appeared, difficulty in breathing was experienced, and cyanosis of the hands and feet set in. Other symptoms typical of reactions seen in protein sensitive individuals appeared. Epinephrine hydrochloride solution 1 c.c. was given hypodermically with resulting rapid improvement in the patient's condition.

The case was reported to show that it is probably not safe to administer pantopon to individuals giving a history of idiosynerasy to morphine.

Burgess, J. F., and Usher, B.: On Hypersensitiveness to Quinine. Canad. M. A. J., **23**: 45, 1930.

In Canada, an increasing number of cases of dermatitis of the face, associated with the use of after-shaving lotions, have been noted.

Canadian law requires that where alcoholic lotions are prepared, either quinine or diethylphenylthalate must be added as a denaturant. Shaving lotions with diethylphenylthalate denaturant were used almost exclusively by two hundred normal patients, i.e., patients giving no history of dermatitis from shaving lotion were tested by the contact method of skin test to solutions of the ingredients used in shaving solution (called for convenience "X"). As a check, tests were also made with a sample of X and a sample of another lotion Y that contained 0.5 per cent colocynth as a denaturant in place of quinine. Results showed only one positive reaction to quinine. This patient also gave a positive reaction to X lotion and a negative one to Y lotion. It is inferred from these tests that a natural idiosyncrasy to quinine does not commonly exist.

Study of numerous cases of X dermatitis revealed the fact that nearly all the cases had applied and rubbed in an after-shave lotion over a period of time before developing any eruption, so that there was no question of an idiosyncrasy, but of a gradually developing sensitization. In all the cases of X dermatitis studied, quinine was the only ingredient that caused the eruption. It is recommended that, in view of the widespread use of after-shaving lotions, some substance other than quinine should be used for a denaturant.

Morenas, L.: Spasmodic Coryza and Conjunctival Crises; Anaphylactic Reactions to Oxyuris. Lyon Méd., **145**: 405, 1930.

A case report is given of a patient suffering over a period of years from oxyuris infection. The patient likewise suffered from coryza and conjunctival crises. These attacks were, in her observation, preceded by and concurrent with a sharp flare-up of the symptoms associated with oxyuris. There was no family history of allergy. Examination of the blood showed a 6 per cent eosinophilia.

Treatment for the oxyuris was instituted, which proved temporarily successful. With the disappearance of the infection, there was a cessation of the coryza and the conjunctival crises. The oxyuris recurred several times and with it the coryza and conjunctivitis. When the report was made, the patient had been free from symptoms for a period of two years.

This case is compared with one reported by Herta Gätz in 1927, in Berlin, in which the patient with no allergic history suffered from coryza and likewise from oxyuris infection. There was an 8 per cent blood eosinophilia. Skin tests with extract of oxyuris gave strongly positive reactions. The oxyuris yielded to treatment, and simultaneously the coryza disappeared. The theory is advanced that both of these cases are examples of anaphylaxis to parasitic toxins.

Research on Asthma. London Correspondent, J. A. M. A., **95**: 422, 1930.

Investigations to date of the Asthma Research Council in Great Britain show that the majority of asthmatics suffer from some constitutional abnormality varying with the individual. Biochemical studies brought to light the fact that a protein substance can be isolated from the urine of asthmatic patients. This substance, applied to the patient's skin, produces wheals, indicating specific sensitivity. The substance, injected into the patient, produces attacks of asthma. Attempts at desensitization by graduated injections of the specific protein were made, and the reports to date are encouraging.

A clue to the nature of the infections liable to cause asthma is suggested by the evidence which has accumulated to show that histamine-producing bacteria are common in the intestinal and respiratory tracts of asthmatics. Of fifty-five patients with allergic asthma treated with dextrose and ammonia to combat the intestinal condition, twenty-seven had no attacks, twenty-five were improved, and three were unchanged.

Jumon, H.: Infantile Asthma. Presse méd., **38**: 1138, 1930.

True infantile asthma, according to the author, appears at any time during the first year of life up to six years of age, and usually subsides spontaneously at about eight or ten years of age or at puberty. Asthma, certain pruriginous dermatoses and hepatic disturbances in children of the above-mentioned ages, form a homogeneous clinical group. They do not all appear simultaneously in the same child, but it is usual for two or three to appear successively or alternately in the same patient. Occasionally only one of the group will appear. This, however, is rare. The majority of the patients are of a thin, pale type, physically rather underdeveloped. Two mechanisms are involved, each possible according to the individual case, i.e., anaphylactic shock and colloidal shock. In asthmatic crises in very young children, anaphylactic shock is relatively rare. In the majority of cases it is a question of colloidal shock, able to arise independently of any penetration into the organism of a foreign substance. The cause of setting off the reflex may be emotion, fatigue, excesses in eating or meteorologic changes, sudden changes in temperature.

In the cases of dermatoses the same two mechanisms are involved, an anaphylactic alimentary shock being more frequent than colloidoclasis. In cases of hepatic disturbances the origin of the shock may usually be found in the introduction through the digestive tract of heterogeneous albumins—chocolate, beans, cream, cakes, etc.

It is noted, however, that in numerous cases it is not possible to isolate the offending cause of the asthma, dermatosis or hepatic disturb-

ance. This is offered as proof that behind the localized reactions there is something else, and that the true origin is, in profound troubles of long standing, bound up with the serum plasma. In short, there is an alteration of nutrition, either hereditary or acquired, that predisposes the organism to factors otherwise harmless.

The prognosis in infantile asthma is good, the trouble usually disappearing spontaneously by the tenth year. General therapy should be directed toward the improvement of the alimentary system. Care should be given to diet and to the avoidance of irritating climatic conditions.

Lehner, E., and Rajka, E.: Theory of Allergy of the Skin. Ann. de dermat. et syph., **1**: 261, 1930.

In experiments, the authors find that the skin may be generally sensitized by the depot method; i.e., the introduction intracutaneously of a specific allergen daily or bi-daily into the same spot in the subject's skin. Sensitization is observable, ordinarily, by the fact that the substance injected for the first time near the depot causes, after twenty-four hours, an inflammation. Later, such inflammation can be obtained not only in the proximity of the depot but at a considerable distance. In other words, sensitization has become general. Patients could be thus sensitized to many substances including definite chemical substances such as morphine, atropine, histamine, etc., provided that these latter substances were mixed with autoserum, glucose or cholesterin.

Certain substances, reagins and dereagins, act as an inflammatory process only in allergic individuals. Certain other substances, however, the authors found in both normal and allergic individuals, that exercised an influence on the inflammatory process. These substances, two in kind, they call intermediary substances, which are capable, one of increasing and the other of decreasing the inflammatory reaction.

Caulfeild, A. H. W., Brown, M. H., and Magner, W.: A Study of Tissue Tubercule-Allergy in Skin Transplants. Am. Rev. Tuberc., **21**: 127, 1930.

In the series of experiments, immune guinea pigs were used. Under ether anesthesia, a large section of the abdominal skin was dissected free and placed in warm Ringer's solution until the incision was closed in the donor. Then transplantation was started. The graft was buried under the skin of the recipient. To determine whether or not the skin, removed from an immune animal and grafted into a normal animal, carried with it any specific tissue immunity or allergy, three types of experiments were used:

1. Following injection of bacilli into the graft, the demonstration

for or against mobilization at the site of injection with dissemination throughout the lymphatic system.

2. Following injection of bacilli into the graft, gross and microscopic observations regarding the rapidity and intensity of reaction as compared with the reaction induced by intracutaneous injection in the immune skin, the normal skin and the normal graft.

3. The character of the reaction of the grafted tissue to tuberculin.

The results of these experiments showed:

1. Following injection of bacilli into the immune graft, tubercle bacilli were immobilized in the graft, and their extension throughout the lymphatic system delayed to an extent comparable to the picture found in the immune animal.

2. The reaction following injection of bacilli into immune grafts was usually relatively rapid and intense.

3. Evidence of persisting sensitization of the immune graft to tuberculin was shown by gross swelling and the presence of microscopic infiltration.

Lehner, E., and Rajka, E.: The Indication of Allergy in Urticaria Factitia. Arch. f. Dermat. & Syph., **159**: 172, 1930.

Serum taken from the arm vein of a patient suffering from urticaria factitia was injected intracutaneously (0.1 c.c.) into the skin of two normal patients. Normal serum was used for a control. Both sera upon injection gave the same sized wheal. Twenty-four hours later, a mechanical stimulus of equal intensity was applied next to both sites of injection. Within five minutes, wheals arose at both sites. Measurements showed that in both normal skins a much larger wheal was raised at the site of injection of the serum from the urticarial patient. According to the authors, the greater urticarial reaction is to be explained only by a carrying over of reagins from the sensitized serum. Further experiments were carried out to find whether or not the so-called intermediary substance which plays a rôle in the inflammatory process is identical with the reagin. Results showed that the substance is not identical.

Similar experiments in desensitization show the presence of dereagins and an intermediary substance which plays a rôle in the decrease of the inflammatory process.

Moore, E. E., and Moore, M. B.: Chemical Studies on Pollen and Pollen Extracts. I. Distribution of Nitrogen Extracted by Various Solvents. J. Am. Chem. Soc., **52**: 3591, 1930.

There is in the literature only very limited information on the subject of pollen composition. As proteins usually are considered the offending agents in allergy, the subject was approached by experi-

ments to determine the nitrogen extractable by various solvents. Four pollens were chosen: timothy and orchard grass and short ragweed and giant ragweed. The solvents used were:

(a) Ether
(b) Water
(c) Salt solution (10 per cent sodium chloride at 60°)
(d) Alcohol solution (75 per cent)
(e) Alkaline solution (0.2 per cent sodium hydroxide)

No heat or concentrated solutions of electrolytes were used. Small samples (2 to 4 grams) of pollen were used. Nitrogen determination by the modified micro-Kjeldâhl method of Koch and McMackin gave accurate estimation of the nitrogen in these solutions. Nitrogen was determined on each extract and on the original pollen and the residue. Results showed that only a very small amount of nitrogen was extracted by ether and that this was probably nonprotein in nature. However, there is some indication in the work of Milford that this fraction may be of allergic importance. The greatest percentage of nitrogen extractable by the solvents used appeared in the water solution, but the indication was that the greater part of this was nonprotein. The nitrogen extracted by salt solution was small in amount and a considerable portion was dialyzable. The fractions soluble in water and diluted salt solutions were considered the most important ones as causative agents in allergy.

A small amount of nitrogen was extracted in the alcohol solution, but no determination was made as to its protein or nonprotein nature.

A small amount of nitrogen was extracted by the dilute alkali solution. About one-half of the nitrogen originally present in the pollen remained in the residue after extraction in the solvents, but this nitrogen was not considered of allergic importance.

The grass pollens swelled in alkali; the ragweed pollens did not. The ragweed pollens contained much more ether-soluble material but only about one-half as much water extractable material. Differences in nitrogen content of similar fractions of the different pollens did not appear significant.

Cantarow, A: The Diffusibility of Calcium in Bronchial Asthma and Allied Disorders and in Pulmonary Tuberculosis. Am. J. M. Sc. **179**: 497, 1930.

It is generally considered that there is something in the make-up of the asthmatic patient which renders him susceptible to the actions of proteins, climatic change, and physical and chemical irritants. Many theories have been advanced to account for the basis of this susceptibility. Calcium deficiency is one of these. It is known that calcium therapy has often a beneficial effect in allergic cases. Opposi-

tion to the theory is based upon the fact that a calcium deficiency has not been satisfactorily demonstrated. Most of the experimental work in this direction has been concerned with the calcium content of the blood serum of atopic individuals. The majority of the evidence points to the fact that in most of these cases the blood serum calcium is within normal limits. What to some extent has been overlooked, however, is the fact that this does not justify the conclusion that there is no disturbance of the calcium balance in such cases. The normal serum calcium concentration is from nine to eleven mg. per 100 c.c. This is made up of two states: diffusible and nondiffusible, the diffusible fraction being that portion capable of passing through the capillary walls and the cell membranes. In addition a portion estimated at about 20 per cent of the total probably exists in ionized form, the remainder being un-ionized. Any alteration of the ratios of the diffusible to the nondiffusible and the ionized to the un-ionized may occur without any change in the amount of the total serum calcium. Thus, the amount of serum calcium is not always a true index of the state of the calcium balance.

Experiments were carried out to determine the diffusibility of calcium in twenty-five patients with bronchial asthma, three with mucous colitis, two with vasomotor rhinitis, one with angioneurotic edema, and sixty-three with pulmonary tuberculosis. The method consisted in the determination of the calcium content of blood serum and cerebrospinal fluid withdrawn at the same time in each case. Calcium determinations were made by the Clark-Collys modification of the Kramer-Tisdall procedure. The difference between the spinal fluid calcium which is diffusible and the total serum calcium gave the diffusible fraction. Results showed the spinal fluid calcium ranged from 4.39 to 6.33 mg. per 100 c.c., twenty being above and one below normal. The nondiffusible calcium ranged from 1.5 and 7.5 mg., two being above and twenty-two below normal. The ratio of diffusible to nondiffusible calcium was from 68.9 to 400 per cent, twenty-three being above and two below normal. Factors other than the diffusibility of calcium which might influence its concentration in the cerebrospinal fluid, such as an inflammatory condition of the brain or meninges, or changes in the intracranial venous and arterial pressures, were controlled and eliminated.

The findings are considered indicative of a state of increased calcium diffusibility in atopic disorders. In experiments by Brown and Ramsdell, with guinea pigs, there was a considerable increase in the diffusible fraction of serum calcium, the total calcium being essentially unaltered. The artificial membrane method was used.

In tuberculosis, as in bronchial asthma and allied disorders, there appeared to be a definite relationship between calcium diffusibility and cell permeability. In chronic pulmonary tuberculosis, there was a

considerable variation in the diffusibility of calcium, an increased diffusibility ratio being associated with an exudative type of lesion with a high degree of clinical activity and a decrease diffusibility being associated with a productive process relatively benign clinically.

Tiefensee, K.: Experiments on the Acid-base Equilibrium in Bronchial Asthma. Deutsches Arch. f. klin. Med. **165**: 265, 1929.

Blood was drawn in a Luer syringe from the cubital vein. The alkaline reserve in CO_2 volume per cent was determined according to the method of Van Slyke. The blood P_H was determined with the potentiometer. Forty cases of asthma in different stages were studied, so that over one hundred individual experiments were made. Results showed that in asthmatics who were free from attack the acid-base equilibrium was normal. That is, the P_H was between 7.3 and 7.5 and the alkaline reserve fifty to sixty volumes per cent. However, during attacks, the acid-base equilibrium moved to the alkaline side, and the blood reaction was either on the upper border of normal or was abnormal by low P_H.

Experiments were performed to influence the alkalinity of the blood in asthmatics, to lower the alkaline reserve and change the blood reactions. This was attained by fasting and acid food with and without the adjunct of acid salts like ammonium chloride and primary ammonium phosphate. The result was relief from asthmatic attacks for the patient.

The simplest and surest method of changing the blood reaction toward the acid side is breathing with carbonic acid air mixtures. Before and after breathing, the alkaline reserve and P_H of the blood is taken in a mixture of 5 to 8 per cent carbonic acid mixture; analysis showed no appreciative change of the alkaline reserve but a distinct displacement of the P_H to the acid side. Through this acidifying of the blood reaction it was shown that an asthmatic attack could be controlled.

Chargin, L., Sulzberger, M. B., and Crowley, D. F.: Hypersensitiveness of the Skin to Arsphenamine as Determined by the Contact Test. Archives of Dermatology and Syphilology **22**: 237, 1930.

The study was made to ascertain whether the disposition for the development of arsphenamine dermatitis could be determined in advance by means of a skin contact test. The contact test was used rather than the intradermal or the scratch method because by both of the latter methods, in a certain percentage of cases, the subject could become sensitized. Such sensitization might lead to serious results upon subsequent intravenous arsphenamine injections.

Five hundred and three patients were used. Two hundred and ten were syphilitic and two hundred and ninety-three nonsyphilitic. All were ward patients whose reactions could be observed over a considerable period of time.

A one-half inch square of cloth was soaked in a 10 per cent solution of neutralized arsphenamine and applied to an intact area of skin on the patient's back. The patch was kept in place for twenty-four hours and then removed and the reactions were read. From several days to one week following these tests the usual courses of arsphenamine treatment were given the patients.

Observations of the skin tests showed positive reactions in 21 per cent of the nonsyphilitic patients and in 17 per cent of the syphilitic patients. Among the patients treated two cases of typical arsphenamine dermatitis were observed. Neither of these cases had had a positive reaction to the skin contact test, and in neither case was any reaction of the test site observed at the time of the development of the dermatitis. None of the patients who had given positive skin contact tests developed dermatitis on subsequent injections of arsphenamine.

The conclusion is drawn that the contact test as used in the study does not indicate whether arsphenamine dermatitis is likely to develop in a patient. No marked differences in sensitiveness between syphilitic and nonsyphilitic groups were noted.

Case reports are given of the two patients who developed dermatitis.

Editors' Note

The editors regret that because of faulty transcription of the discussion of some of the papers read before the Society for the Study of Asthma and Allied Conditions at Atlantic City on May 3, errors appeared. The discussions were published in the July issue of this journal, and the following corrections should be made:

Page 463, line 5, should read "aside from the mere quantitative difference" instead of "aside from the mere point of difference."

Page 465, the discussion of Dr. Levine should read as follows: "The experiments of Miss Bowman and Dr. Walzer on the study of the relationship of the danders of horse, donkey and zebra are interesting in the light of the work done by Landsteiner and van der Scheer on the immunologic relationship of the blood serum and cells of two of the three species mentioned. These authors found that it is comparatively easy to differentiate the blood cells of the horse and donkey by means of absorbed anti-horse or anti-donkey agglutinins produced by the injection of the blood cells into rabbits. Also the serum proteins of these two animals could be differentiated by means of the precipitin reaction, but the differences observed were not considerable.

"Miss Bowman and Dr. Walzer have at their disposal another method to tackle problems of this kind. It is interesting that according to their reactions the danders of the horse, donkey and zebra could be differentiated from each other."

Page 475, line 8, should read "Freund" instead of "Froin."